The Journal of the American Medical Association

Published Under the Auspices of the Board of Trustees

Vol. 144, No. 16 — Chicago, Illinois — December 16, 1950
Copyright, 1950, by American Medical Association

EFFECT OF CORTISONE AND PITUITARY ADRENOCORTICOTROPIC HORMONE (ACTH) ON RHEUMATIC DISEASES

PHILIP S. HENCH, M.D.
CHARLES H. SLOCUMB, M.D.
HOWARD F. POLLEY, M.D.
and
EDWARD C. KENDALL, Ph.D.
Rochester, Minn.

The antirheumatic effects of the adrenal cortical hormone, cortisone, and of the pituitary adrenocorticotropic hormone (ACTH; corticotropin) have been demonstrated by many investigators within the past year. These beneficial effects may be produced especially on rheumatoid arthritis and acute rheumatic fever but also on several other articular conditions such as the acute arthritis of gout, the arthritis of disseminated lupus erythematosus, of psoriasis, of ulcerative colitis and to a limited extent on the arthritis of tuberculosis and in certain cases of primary osteoarthritis. In general the relief lasts only during the period of hormonal administration.

GENERAL RESULTS IN RHEUMATOID ARTHRITIS

Varying degrees of improvement have been obtained in practically all cases of active rheumatoid arthritis, rheumatoid spondylitis and Still's disease (juvenile rheumatoid arthritis) in which cortisone and pituitary adrenocorticotropic hormone have been used. Most patients, even those with severe but reversible disease, have promptly obtained decided relief. Other patients whose chronic or severe disease had produced irreversible anatomic changes have been less notably benefited. It appears that in the cases in which disappointing results were obtained small and relatively ineffective doses sometimes were used in an attempt to reduce the expense of the rather costly hormones; occasionally relatively inactive nonstandardized preparations of pituitary adrenocorticotropic hormone were used, and in a few cases the patients' adrenal glands were found (by use of the eosinopenic test of Thorn) to be poorly responsive to pituitary adrenocorticotropic hormone and therefore unable to produce sufficient amounts of endogenous cortisone to provide a satisfactory result.

From the Division of Medicine, Mayo Clinic (Drs. Hench, Slocumb and Polley) and from the Division of Biochemistry, Mayo Foundation (Dr. Kendall).

Read in the Symposium on ACTH and Cortisone before the Section on Experimental Medicine and Therapeutics at the Ninety-Ninth Annual Session of the American Medical Association, San Francisco, June 28, 1950.

In our first series of cases[1] of rheumatoid arthritis, in all of which the disease was severe, the antirheumatic effect was very marked (almost complete relief) in 12 (57 per cent) of the 21 cases in which cortisone was given, marked (75 to 90 per cent relief) in 8 (38 per cent) and moderate in 1 (5 per cent). The antirheumatic effect was very marked in 4 (67 per cent) of 6 cases in which pituitary adrenocorticotropic hormone was given and marked in the remaining 2 (33 per cent).

GENERAL PLAN OF DOSAGE

Cortisone.—Cortisone[2] was given as a crystalline suspension injected intramuscularly. The initial day's dose was 100 mg. in our first cases and 300 mg. (150 mg. into each buttock) in later cases. Thereafter 100 mg. was the usual daily dose. A single daily dose of 100 mg. appeared to be as effective as 50 mg. twice a day. On special occasions 150 or 200 mg. was given daily for two to five weeks. In our cases of severe rheumatoid arthritis daily doses of 75 mg. were usually incompletely effective; smaller doses were inadequate or totally ineffective. It recently has been observed that mild or moderately severe rheumatoid arthritis usually can be controlled satisfactorily by giving full doses until the disease is largely suppressed and thereafter by giving 35 to 65 mg. a day or 100 mg. on three days a week, such as Monday, Wednesday and Friday.[3]

Pituitary Adrenocorticotropic Hormone.—Daily doses of pituitary adrenocorticotropic hormone,[4] prepared as a fluffy powder which is dissolved in saline solution and given intramuscularly, in our cases were usually 100 mg., occasionally 45 to 140 mg. Since the drug is rapidly absorbed and utilized by the body the total daily dose must be given in divided amounts every six or eight hours. After the initial full suppressive doses have been given daily for two or three weeks, or until symptoms are largely controlled, smaller daily doses may maintain the improvement.

Recent preparations of the drug have been about twice as potent as cortisone, milligram for milligram; thus the antirheumatic effect of about 40 mg. of pituitary adrenocorticotropic hormone is about equal to that of 100 mg. of cortisone. In general, early suppressive

1. Hench, P. S.; Kendall, E. C.; Slocumb, C. H., and Polley, H. F.: Effects of Cortisone Acetate and Pituitary ACTH on Rheumatoid Arthritis, Rheumatic Fever and Certain Other Conditions: A Study in Clinical Physiology, Arch. Int. Med. **85**: 545-666 (April) 1950.

2. Supplied by Drs. Randolph Major, vice president, and James Carlisle, medical director, Merck & Company, Inc.

3. (a) Boland, E. W.: The Effects of Cortisone and Adrenocorticotropic Hormone (ACTH) on Certain Rheumatic Diseases, California Med. **72**: 405-414 (June) 1950. (b) Boland, E. W., and Headley, N. E.: Management of Rheumatoid Arthritis with Smaller (Maintenance) Doses of Cortisone Acetate, J. A. M. A. **144**: 365-372 (Sept. 30) 1950. (c) Freyberg, R. H.: Effects of Cortisone and ACTH in Rheumatoid Arthritis, Bull. New York Acad. Med. **26**: 206-211 (April) 1950.

4. Supplied by Dr. John R. Mote, medical director, the Armour Laboratories.

doses of the former drug would be about 40 to 60 mg. daily; maintenance doses, about 15 to 20 mg. daily. In the light of further experience it seems that the maintenance doses of the two hormonal agents used in our first series of cases were sometimes larger than necessary. The doses of the two hormones must be individualized.

PATTERN OF CLINICAL RELIEF

Clinical Response.—The initial pattern of clinical improvement was characteristic. Lessening of subjective symptoms began usually within two or three days, sometimes within a few hours after the first injection of one or the other hormone. Within a few days there were appreciable reduction of muscular and articular stiffness, lessening of articular tenderness, aching and pain on motion, and usually reduction of articular swelling. In general, within the first week stiffness, aching and pain on motion were greatly relieved; within the second week articular tenderness was reduced or disappeared and articular swellings began to diminish.

Thereafter, the use of either of the hormones being continued, further improvement was more gradual, sometimes being interrupted by minor flares, "arthritis in miniature." The maximal over-all improvement sometimes developed after two or three months of administration of the hormones.

Patients often noted, coincident with the improvement of joints and muscles, increased strength, a sense of lessened toxemia, improved nutrition with increased appetite and nutritional gains in weight, and euphoria or a sense of well-being which often expressed itself by increased mental and physical energy. Fever, if present, usually disappeared. Rheumatoid nodules and enlarged lymph nodes sometimes diminished in size; a few small ones seemed to disappear. Flexion contractures usually diminished; if they were not too long established they often disappeared, frequently within three weeks.

Biochemical and Metabolic Effects.—Sedimentation rates were reduced, often to normal values. The concentrations of hemoglobin of anemic arthritics often increased, as did erythrocyte counts. Total leukocyte counts usually increased slightly. Eosinophil counts were decidedly reduced by pituitary adrenocorticotropic hormone, but were not altered consistently by cortisone. When hyperglobulinemia was present, reduction of serum globulin usually occurred and albumin-globulin ratios tended to return toward normal. Urinary 17-ketosteroids were reduced by cortisone (100 mg. doses) and decidedly increased by pituitary adrenocorticotropic hormone. The excretion of corticosteroids in urine was increased by either hormone.

Daily doses of 100 mg. of cortisone usually did not produce significant alteration in the concentrations of electrolytes in blood or tissues, but the administration of 200 mg. of the drug daily for two weeks or more sometimes produced an increased excretion of potassium and chlorides with a resultant hypopotassemic, hypochloremic alkalosis.[5]

Histological Changes.—Biopsy of synovial tissues removed before and at various times during the use of either of the hormones indicated that synovial inflammation was reduced thereby. Histological improvement was mild, moderate or pronounced, depending on how long the hormones were given and on the patient's individual response to them. The synovial tissues, though practically always improved, were not fully restored to normal. Improvement consisted of reduction in the cellular reaction with decreased number of plasma cells and lymphocytes, reduction of papillary tufting, reduction or absence of deposition of fibrin, lessened edema, and evidence of fibrous healing.

WITHDRAWAL OF THE HORMONES

When the use of cortisone or pituitary adrenocorticotropic hormone was discontinued, rheumatic activity returned rather quickly in about 75 per cent of our cases, but in about one fourth of the cases the relapses were delayed for some months. These will be reported in the section on "Optimal After-Effects."

SIDE EFFECTS OF THE HORMONES

Incidence.—These potent hormones are capable of affecting many bodily functions and many tissues other than those of joints and muscles. Some of the results are desirable but others are not. About 40 per cent of our first group of patients had no significant side effects; these patients received cortisone or pituitary adrenocorticotropic hormone for three weeks to four and a half months. Mild side effects such as mild acneform eruption, mild hypertrichosis, rounding of the face or mild irritability developed among 35 per cent of the patients who received one of the hormones continuously or almost continuously for 11 days to seven months. More disturbing side effects developed in the remaining 25 per cent during the administration of one of the hormones 12 to 187 days.

The undesirable effects usually developed in patients who received the hormones in what we now regard as high doses (200 mg. of cortisone or 100 mg. of pituitary adrenocorticotropic hormone daily) or received smaller doses, usually 100 mg. of cortisone daily, for relatively long periods. Individual tolerance also played a role, and men tolerated the two hormones better than women, especially adolescent or menopausal females.

Types.—The commoner side effects consisted of minor alterations of psyche (euphoria, mild nervousness and restless energy) and certain transient paresthesias or somatic symptoms resembling those considered functional. The paresthesias and somatic symptoms may have resulted from transient vasomotor changes or transient alterations in tissue fluids and electrolytes. Some rounding of the face was encountered not infrequently. Occasionally mild hypertrichosis, transient decrease of libido or some muscular weakness and lassitude developed; the last two were sometimes associated with hypopotassemic hypochloremic alkalosis, sometimes not.

These hormones may induce retention of salt and water indicated by sudden gains in weight with or without visible edema. Cortisone appears to possess this property less than does pituitary adrenocorticotropic hormone; this may or may not be a matter of relative dosage. When significant retention occurred, it usually developed early in the course of hormonal usage. Sometimes some degree of fluid retention persisted as long as the hormones were given, but more often an initial retention was transient and soon disappeared even though dosage was unchanged. Two patients who received cortisone had acneform eruption or folliculitis. Amenorrhea, red striae over thighs and increased retrocervical fat (buffalo hump) each developed in 1 case.

5. Sprague, R. G.; Power, M. H.; Mason, H. L.; Albert, A.; Mathieson, D. R.; Hench, P. S.; Kendall, E. C.; Slocumb, C. H., and Polley, H. F.: Observations on the Physiologic Effects of Cortisone and ACTH in Man, Arch. Int. Med. **85**: 199-258 (Feb.) 1950.

Although these hormones, especially pituitary adrenocorticotropic hormone, may notably increase the blood pressure of patients with hypertension, renal disease or conditions associated with renal lesions (for example, disseminated lupus erythematosus), significant increases of blood pressure did not develop in any of our rheumatoid patients.

Exceedingly large doses of either hormone may induce hyperglycemia and glycosuria in rats. These hormones, in certain doses and under certain conditions, may temporarily impair carbohydrate tolerance. It would appear, however, that either hormone, given in the dose range used in our cases to rheumatoid patients without latent or frank diabetes, does not reduce carbohydrate tolerance to a clinically significant degree. Whatever impairment of carbohydrate tolerance may have resulted from cortisone therapy in our patients was slight. During the use of cortisone abnormal sugar tolerance tests were noted in 5 cases, but in none of our cases did significant glycosuria or fasting hyperglycemia develop. Diabetes and rheumatoid arthritis seldom coexist, but for rheumatic or nonrheumatic patients with latent or frank diabetes these hormones should be expected to induce more pronounced reduction of carbohydrate tolerance. Such a case, that of a diabetic patient with rheumatoid arthritis, was recently reported.[2b]

One of the more interesting effects of these hormones is that on the psyche of rheumatic or nonrheumatic (nonpsychotic) patients. Rome and Braceland [6] have described four categories which encompass the range of psychologic response which attends this treatment. In grade 1 are included those patients who respond to the symptomatic relief with a feeling of well-being, a sense of increased physical and psychological capacity for constructive work which is proportionate to the subjective and objective changes produced. Several of our patients with rheumatoid arthritis may be placed in this category. A response, grade 2, differs only in its quantitative aspects. The thinking and behavioral processes are more accelerated, the amplitude of mood change is greater, and it is evident grossly that these patients are stimulated. Such responses were experienced by several of our rheumatoid patients. A grade 3 response is prone to develop in those nonrheumatic or rheumatic patients whose personality appraisals reveal evidence of previous and severe psychologic conflict. Their response to either hormone is descriptively similar to their past response to environmental stress of different sorts. Patients with cyclothymic personalities experienced mild hypomania or mild depressions, or both, whereas the obsessive person tended to have phobia states and other ruminative preoccupations. We have seen such a reaction by only 1 rheumatoid patient, a woman who received 100 mg. of cortisone daily for 187 days; after about five months changes in mood and then depression developed. These disappeared rather quickly after the use of cortisone was discontinued.

A grade 4 response is a relatively rare sequel. It has not been encountered in our cases of either rheumatoid arthritis or rheumatic fever. It comprises overtly psychotic responses characterized by delusionary thinking, hallucinations, confusion, mood appropriate to the content of thought and an acceleration in the stream of mental productivity. It is of brief duration, and after the discontinuation of hormonal therapy the grossly psychotic symptoms and signs subside within two weeks. Again there is evidence that the most prominent factor in the determination of this response is the patient's prepsychotic personality.

In summary, the physical, biochemical and metabolic changes which these hormones induce constitute, according to Rome and Braceland, a radical change in the integration of the entire organism. This change assumes the proportions of a stress comparable to the more usual physical and environmental stresses which provoke these same kinds of psychologic reactions in equally vulnerable persons. How a given rheumatic or nonrheumatic patient may react psychologically to one of the hormones can be found in an appraisal of the manner in which he has adjusted previously to other stress situations, such as severe fever, acute or chronic illness, financial, domestic or personal difficulties. Rheumatoid patients seldom have psychotic reactions as a result of the pains, frustration, economic insecurity, fear of dependency and therapeutic adventures which their disease entails. Hence, one would hardly expect a grade 4 reaction to the "stress" provided by the use of these hormones. Although grade 4 reactions have been observed in 1 of our cases of severe psoriasis and psoriatic arthritis and in 3 of severe disseminated lupus, such reactions have not been encountered so far among our cases of rheumatoid arthritis.

Posthormonal (Withdrawal) Phenomena.—In several of our patients about two or three weeks after withdrawal of hormones muscular weakness and fatigue developed, lasted two or more weeks and then disappeared. In these cases the use of cortisone or of pituitary adrenocorticotropic hormone had been discontinued abruptly without tapering off the doses. Temporary reduction of function of the adrenal cortex was considered a possible cause.

Theoretical Possibilities.—Repeated injections of pituitary adrenocorticotropic hormone produce adrenal hypertrophy, and repeated injections of cortisone produce adrenal atrophy. Hence it has been suggested that the stimulation of adrenal glands by the former drug or the inhibitive effect of exogenous cortisone on the adrenals beyond a certain limit might lead to a temporary or to a more or less permanent exhaustion of the adrenal cortex which could be serious in the face of subsequent stress. Further experience will determine the likelihood of such possibilities. But the known recuperative powers of adrenal glands which have been atrophic for years in consequence of long-standing (pituitary or adrenal) Cushing's disease permit one to conjecture that the prolonged use of exogenous pituitary adrenocorticotropic hormone or cortisone, if given in amounts that can be shown to be not too excessive physiologically, will not induce irreversible clinicopathological consequences.

Reversibility and Control of Side Effects.—All the reported side effects observed to date by us and others have been transient and reversible. In most instances the reversibility has developed rapidly as soon as the doses were reduced in amount or discontinued. Control of side effects will be discussed later in this paper.

USE OF HORMONES IN OTHER RHEUMATIC AND ARTICULAR CONDITIONS

For reasons stated elsewhere [1] we have given cortisone or pituitary adrenocorticotropic hormone to patients who had other rheumatic and articular conditions besides rheumatoid arthritis.

6. Rome, H. P., and Braceland, F. J.: Use of Cortisone and ACTH in Certain Diseases: Psychiatric Aspects, Proc. Staff Meet., Mayo Clin. 25: 495-497 (Aug. 16) 1950.

Acute Rheumatic Fever.—With our colleagues, Drs. Barnes and Smith,[7] we have given cortisone or pituitary adrenocorticotropic hormone to several patients who had acute rheumatic fever and to a few who had severe rheumatic carditis and cardiac failure. Daily doses of the former were usually 200 mg. for the first several days, later usually 100 mg.; total doses ranged from about 1.2 to 7.4 Gm. within three to nine weeks. Daily doses of the latter were 25 to 60 mg. for the first several days, usually 45 mg.; later daily doses decreased to 10 to 15 mg. Total doses ranged from 409 mg. to 1.4 Gm. given within two to eight weeks.

The acute manifestations of rheumatic fever were quickly abolished. Fever, acute polyarthritis and tachycardia usually disappeared within five days or less. Prolonged P-R intervals in the electrocardiogram usually became normal within three weeks or less. Sedimentation rates and hyperglobulinemia were reduced; rates became normal in an average of about 18 days. When the hormones were not given long enough there were short, usually mild, rheumatic recurrences: these consisted sometimes of transient increases of sedimentation rate, pulse rate or P-R interval, or all three, without fever or articular symptoms; sometimes the fever and articular symptoms also recurred. When the hormones were given again these recurrences disappeared.

What might be called the acute rheumatic state (that period during which the unknown irritant of rheumatic fever operates to produce in affected responsive tissues inflammatory reactions of an exudative and proliferative type) may last about six to 12 weeks. The hormones do not remove this irritant, hence they do not shorten the acute rheumatic stage. However, they appear to protect the affected tissues against the irritant; consequently the abnormal physiological processes which characterize the disease subside, and the clinical and laboratory manifestations disappear. This protection continues as long as the hormones are administered, even though the underlying and now essentially symptomless acute rheumatic state has not yet run its course.

With this concept in mind it can be understood why hormones must be given (or if their use has been discontinued prematurely, readministered) until persistently negative clinical and laboratory data indicate that the acute rheumatic state has passed. Because cardiac muscle and fibrous tissue of heart valves are not much different from the skeletal muscle and fibrous tissues which are so promptly benefited in rheumatoid arthritis, it is hoped that the proper use of these hormones may prevent or modify the development of the cardiac complications of acute rheumatic fever. Reexamination of the hearts of these patients several months after use of the hormones was stopped revealed no definite evidence of new or increased old rheumatic carditis [7b,c] except in 2 patients, each of whom had just experienced another attack of acute rheumatic fever. To prevent such recurrences our revised policy involves consideration of chemoprophylaxis. There is reason to hope that the combination of hormonal usage during the acute stage of the disease plus the subsequent prophylactic oral use of penicillin or sulfonamides may provide greater cardiac protection than has been possible heretofore. Further prolonged observations must be made to determine the value of such a plan. Further data on this problem are being reported elsewhere.[7c]

Other Articular Conditions.—In several cases of lupus erythematosus disseminatus use of either of the hormones was accompanied with temporary disappearance not only of arthritis but also of fever, skin reactions, pericarditis, pleurisy and leukopenia.[8] Renal lesions and albuminuria, if present, appeared to be unaffected. Sometimes severe cardiac lesions have been unresponsive and blood pressure has increased. Although these hormones have not been as beneficial in lupus erythematosus disseminatus as in rheumatoid arthritis, they appear to be helpful often, perhaps even life saving in acute crises. Temporary remissions, not cures, were induced.

Psoriatic arthritis has been, in our experience, more responsive to these hormones than the associated psoriasis, which has disappeared temporarily when fairly large doses were given.[9] In tuberculous arthritis (two cases) articular symptoms and signs and sedimentation rates decreased notably but results of articular biopsy, guinea pig test and cultures remained positive.

To conserve the hormones for use in more serious conditions they have been administered by us or others in only a few cases of osteoarthritis. One of our patients with leukemia and preexisting primary osteoarthritis obtained from cortisone articular relief which was maintained for some time after use of the hormone was discontinued. The articular symptoms and sometimes the intestinal symptoms of chronic ulcerative colitis have been responsive to these hormones in some cases.[10]

Independent investigations on the effect of pituitary adrenocorticotropic hormone on quiescent gout and acute gouty arthritis have been carried out by Robinson, Conn, Block, Louis and Katz,[11] by Hellman [12] and by Wolfson and his associates.[13] A close relationship between gouty arthritis and the function of adrenal cortex was demonstrated. Pituitary adrenocorticotropic hormone provoked attacks of acute gouty arthritis in patients with quiescent gout but also promptly relieved patients with acute gouty arthritis. Rapid amelioration of acute gouty arthritis by the use of this drug or of

7. (*a*) Hench, P. S.; Slocumb, C. H.; Barnes, A. R.; Smith, H. L.; Polley, H. F., and Kendall, E. C.: The Effects of the Adrenal Cortical Hormone 17-Hydroxy-11-Dehydrocorticosterone (Compound E) on the Acute Phase of Rheumatic Fever: Preliminary Report, Proc. Staff Meet., Mayo Clin. **24**: 277-297 (May 25) 1949. (*b*) Barnes, A. R., and Smith, H. L.: The Effects of the Administration of Cortisone and ACTH on Patients with Acute Rheumatic Fever, Mod. Concepts Cardiovas. Dis. **19**: 59-60 (Feb.) 1950. Barnes, A. R.: Effects of Cortisone and ACTH in 14 Patients with Acute Rheumatic Fever, Proc. Staff Meet., Mayo Clin. **25**: 478-479 (Aug. 16) 1950. (*c*) Barnes, A. R.; Smith, H. L.; Slocumb, C. H.; Polley, H. F., and Hench, P. S.: The Effect of Cortisone and ACTH on the Acute Phase of Rheumatic Fever: Further Observations, unpublished data.

8. Brunsting, L. A.; Slocumb, C. H., and Didcoct, J. W.: Effects of Cortisone on Acute Disseminated Lupus Erythematosus, Proc. Staff Meet., Mayo Clin. **25**: 479-482 (Aug. 16) 1950.

9. Polley, H. F., and Brunsting, L. A.: Effects of Cortisone and ACTH on Psoriatic Arthritis, unpublished data.

10. Dearing, W. H., and Brown, P. W.: Experiences with Cortisone and ACTH in Chronic Ulcerative Colitis, Proc. Staff Meet., Mayo Clin. **25**: 486-488 (Aug. 16) 1950.

11. Robinson, W. D.; Conn, J. W.; Block, W. D., and Louis, L. H.: Role of the Adrenal Cortex in Urate Metabolism and in Gout, Proc. Central Soc. Clin. Research **21**: 23-24, 1948. Robinson, W. D.; Conn, J. W.; Block, W. D.; Louis, L. H., and Katz, J.: Role of the Anterior Pituitary and Adrenal Cortex in Urate Metabolism and in Gout, Ann. Rheumat. Dis. **8**: 312-313 (Dec.) 1949. Robinson, W. D.; Conn, J. W.; Block, W. D., and Louis, L. H.: Role of the Adrenal Cortex in Urate Metabolism and in Gout, J. Lab. & Clin. Med. **33**: 1473-1474 (Nov.) 1948.

12. Hellman, L.: Production of Acute Gouty Arthritis by Adrenocorticotropin, Science **109**: 280-281 (March 18) 1949.

13. Wolfson, W. Q.; Levine, R.; Cohn, C.; Hunt, H. D.; Guterman, H. S., and Rosenberg, E. F.: Adrenocortical Dysfunction in Gout, Ann. Rheumat. Dis. **8**: 311 (Dec.) 1949. Wolfson, W. Q., and Cohn, C.: The Role of the Pituitary Adrenocorticotropic Hormone (ACTH) and of Adrenal Cortical Steroid Hormones in the Pathological Physiology and Experimental Therapeutics of Clinical Gout, in Mote, J. R.: Proceedings of the First Clinical ACTH Conference, Philadelphia, The Blakiston Company, 1950, pp. 241-283.

cortisone has since been reported by others.[14] Confirmatory observations on the effects of either drug on these various rheumatic and articular conditions have been made by a number of investigators.

MODE OF ACTION

How these two hormones produce their antirheumatic effect is still not clear. Rheumatoid arthritis is not a feature or complication of Addison's disease; indeed, rheumatoid arthritis and Addison's disease seldom coexist. The antirheumatic action of these hormones is not seemingly dependent on any of their metabolic or biochemical effects so far demonstrated. The adrenal glands of most rheumatoid patients under the stimulation of injected (exogenous) pituitary adrenocorticotropic hormone can apparently produce amounts of cortisone or a cortisone-like steroid sufficient to suppress the rheumatic manifestations. How much antirheumatic steroid these adrenals are producing without artificial stimulation or to what extent they are capable of responding spontaneously to sudden increases in tissue needs remains to be determined.

If there is no absolute deficiency of cortisone in rheumatoid arthritis perhaps there is a relative deficiency, one concerned with an increased destruction or with an increased tissue requirement for cortisone rather than with decreased production. Does pregnancy relieve rheumatoid arthritis by an increased production of cortisone or cortisone-like steroid? Does jaundice produce its ameliorating effects by lessening the inactivation or destruction of cortisone or by improving the utilization of cortisone at the tissue level? How does chrysotherapy benefit rheumatoid patients, through some influence on the pituitary-adrenal axis or by an entirely different mechanism involving fibroarticular tissues? Intensive study of these mechanisms of relief should be fruitful.

The fact that the effects of cortisone and pituitary adrenocorticotropic hormone are not disease specific but group specific (for example, antirheumatic and antiallergic) and demonstrable in a number of loosely related conditions (collagen diseases) suggests that the hormones act at the tissue level in some as yet unknown manner. They do not kill germs or cure any of the diseases whose symptoms they suppress; they appear instead to provide the susceptible tissues with a shieldlike buffer against the various irritants.

CLINICAL LIMITATIONS

These hormones (like substance X of jaundice or pregnancy) appear to have the power of controlling or reversing the physiological abnormalities of the diseases under discussion, in consequence of which the tissue reactions subside. These tissue reactions not only provide most of the symptoms of the disease but, if they are long continued, lead to proliferative and reparative histological changes which produce, for example, the "rheumatoid joint" or the chronic rheumatic heart. These reparative changes are responsible for the pathologicoanatomic residues of the diseases, and they are not only largely irreversible but unaffected by cortisone or pituitary adrenocorticotropic hormone. Therefore, to obtain the best results the hormones should be used early, before irreversible changes in tissue have developed. With these distinctions in mind, it will be understood why the hormones may provide much more relief in a case of severe but early reversible rheumatoid arthritis than in a case of old arthritis of relatively slight (physiological) activity, in which articular (anatomical) residues are considerable. So, too, better results have been obtained in severe acute rheumatic fever with acute carditis than in less severe rheumatic fever superimposed on old damaged hearts. In short, it is the disease, not the residues of disease, which these hormones influence beneficially. To use a figure of speech, the hormones act like a fire suppressor or fire shield; they do not extinguish the fire, nor do they act as carpenters to repair the fire's damage.

PRACTICAL CONSIDERATIONS

Before these hormones can assume the role not merely of investigative agents but of acceptable therapeutic measures, certain practical problems must be solved. Sufficient amounts of cortisone and pituitary adrenocorticotropic hormone must become available and optimal methods of administration must be devised whereby the patient may receive the greatest antirheumatic effect at the least cost in terms of unwanted side effects.

Production of the Hormones.—In the matter of production great strides have been made by the two chief manufacturers of these hormones. Production schedules are far ahead of those considered possible a few months ago. Despite the fact that no new source of cortisone and no actual shortening of the method for its partial synthesis have yet been discovered, improvements in several of the 38 chemical procedures required for its production from desoxycholic acid have increased the ultimate yield satisfactorily. Methods for the preparation of pituitary adrenocorticotropic hormone also have been improved, and the potency and purity of current preparations have been increased. Several investigators[15] have developed peptide fragments of the hormone which retain the antirheumatic property, possess a molecular weight of only about 1,000 (as compared to 20,000 for the parent product) and give a basis for hoping that eventual synthesis of a potent peptide fragment may be accomplished. Meanwhile it is reported that the production of cortisone is forty-five times greater and that of pituitary adrenocorticotropic hormone is thirty times greater than it was a few short months ago. Prices have been reduced, other companies with large facilities are entering the field, and the future looks bright. But impatient rheumatic sufferers want the future now. Great efforts have been expended in the search for steroids related to cortisone which might not only be more available and cheaper, perhaps subject to total synthesis, but also possess antirheumatic properties and be devoid of side effects.

14. (*a*) Spies, T. D., and Stone, R. E.: Relief of the Symptoms of Acute Gout and Rheumatoid Arthritis by Means of Pituitary Adrenocorticotropic Hormone, South M. J. **42**: 720-722 (Aug.) 1949. (*b*) Thorn, G. W.; Bayles, T. B.; Massell, B. F.; Forsham, P. H.; Hill, S. R., Jr.; Smith, S., III, and Warren, J. E.: Studies on the Relation of Pituitary-Adrenal Function to Rheumatic Disease, New England J. Med. **241**: 529-537 (Oct. 6) 1949. (*c*) Margolis, H. M., and Caplan, P. S.: Treatment of Acute Gouty Arthritis with Pituitary Adrenocorticotropic Hormone (ACTH), J. A. M. A. **142**: 256-258 (Jan. 28) 1950. Boland.[3a]

15. Li, C. H.: Biochemistry of Adrenocorticotropic Hormone: Review, in Reifenstein, E. C., Jr., and Johnson, V.: Conference on Metabolic Aspects of Convalescence: Transactions of the Seventeenth Meeting, New York, Josiah Macy, Jr., Foundation, 1948, pp. 114-132. Li, C. H.: Relative Size of Adrenocorticotrophically Active Peptide Fragments, Federation Acta endocrinol. **3**: 299-309 (Dec.) 1949. Kinsell, L. W.; Li, C. H.; Results of Administration of Adrenocorticotrophically Active Peptides (ACTH Peptides) to a Patient Suffering from Rheumatoid Arthritis, Acta endocrinol. **3**: 299-309 (Dec.) 1949. Kinsell, L. W.; Li, C. H.; Margen, S.; Michaels, G. D., and Hedges, R. N.: Metabolic Effects of a Peptide Mixture Derived from ACTH (Li) in Comparison with Those Resulting from Whole ACTH Administration in a Human Subject, in Mote, J. R.: Proceedings of the First Clinical ACTH Conference, Philadelphia, The Blakiston Company, 1950, pp. 70-82. Morris, P., and Morris, C. J. O. R.: Isolation of a Polypeptide with High Adrenocorticotrophic Activity: Preliminary Communication, Lancet **1**: 117-118 (Jan. 21) 1950. Astwood, E. B.; Cleroux, A. P.; Payne, R. W., and Raben, M. S.: Therapeutic Studies on Some Newer Corticotrophic (ACTH) Preparations, Bull. New England M. Center **12**: 2-10 (Feb.) 1950. Brink, N. G.; Meisinger, M. A. P., and Foekers, K.: The Activity of a Hydrolysate of Adrenocorticotropic Hormone in Rheumatoid Arthritis, J. Am. Chem. Soc. **72**: 1040-1041 (Feb.) 1950.

Effect of Steroids Related to Cortisone.—Many steroids more or less closely related to cortisone have been prepared for clinical testing. In the Mayo Clinic's section on rheumatic diseases we have tested 12 of them; results have been reported by Polley and Mason.[16] Ten of them belonged, like cortisone, to the Δ^4-pregnene series and differed from cortisone by variations at the carbon-11 or carbon-17 position or at both, by a single change in the side chain, by changes at both carbon-11 and in a side chain or by changes in the degree of saturation in the A and B rings. In other words, several of them were cortisone except for a single alteration. Despite this nine of them were ineffective in rheumatoid arthritis although given in amounts comparable to effective doses of cortisone. Also ineffective in our hands and in those of certain other rheumatologists were two more preparations which were recommended as possible substitutes for cortisone, namely, Δ^5-pregnenolone and 21-acetoxy-pregnenolone, known commercially also as natolone and artisone respectively. Belonging to the Δ^5-pregnene series they are much more distantly related chemically to cortisone than the other ineffective steroids just mentioned. Early favorable reports on progesterone and testosterone propionate have not been confirmed. Several other steroids have recently been reported as being ineffective.[17]

The only steroid besides cortisone that we have found to possess significant or comparable antirheumatic activity is 17-hydroxycorticosterone, Kendall's compound F.[18] Supplies of this material are so scarce that we have been able to give it so far to only 2 rheumatoid patients. It has decided antirheumatic properties, but whether they are greater or lesser than those of cortisone remains to be determined. Since its production is more difficult than that of cortisone compound F offers no early solution to the present problem of inadequate supply.

Effect of Adrenal Cortex Extracts.—We have administered to a few rheumatoid patients four extracts of adrenal cortex.[16] Two were ineffective (Kendall's extract and Upjohn's lipo-adrenal cortex extract, double strength). One concentrated extract (adrenal cortex extract [18] in propylene glycol, twenty strength) possessed mild antirheumatic activity, but a specially prepared highly concentrated extract, given in capsules orally, demonstrated pronounced antirheumatic properties. The potency of this preparation was in all likelihood based on its content of compounds E and F. It is of considerable significahce that this preparation, containing compounds E (cortisone) and F, was potent when given orally. This confirms certain animal experiments which have led to the conclusion that cortisone may be effective when given by mouth.[19]

Effect of Other Substances.—Earlier favorable European and British reports on the supposed effectiveness of desoxycorticosterone acetate given with vitamin C (ascorbic acid) have been outnumbered by more recent unfavorable reports.[20] Use of this combination was investigated by our associate Dr. Paul Bilka,[21] who observed no objective changes or significant effect on sedimentation rates in several rheumatoid patients. Such transient subjective improvement as developed occasionally was no greater than that obtained by giving desoxycorticosterone and vitamin C in half the recommended dosage, by giving desoxycorticosterone followed by an injection of saline solution (without vitamin C) or by giving saline solution (without desoxycorticosterone) followed by vitamin C, or even by giving two consecutive injections of saline solution. The hope that injections of epinephrine might stimulate the production in patients of significant amounts of cortisone has not materialized.[22]

SPECIFICITY OF CORTISONE

The negative results with these various steroids indicate that cortisone possesses a high degree of physiologic specificity approached only by 17-hydroxycorticosterone (compound F of Kendall), which differs from cortisone only in that at the important carbon-11 position there is a hydroxyl radical in place of the ketone group.

ANTIRHEUMATIC PROPERTIES OF STEROIDS

From their study Polley and Mason concluded that the antirheumatic properties of the steroid structure are dependent on the presence of a ketone group at carbon-3, either a ketone or a hydroxyl group at carbon-11, a ketone group at carbon-20, a hydroxyl group at carbon-17 and at carbon-21 and a double bond between carbon atoms 4 and 5.

OPTIMAL DOSAGE AND METHOD OF HORMONAL ADMINISTRATION

Further experience is needed to determine the optimal dosage and methods of administration of cortisone and pituitary adrenocorticotropic hormone. Present procedures are tentative.

Acute Rheumatic Fever.—For the investigative management of acute rheumatic fever the hormones should be given at first in full suppressive doses, perhaps 200 mg. of cortisone or about 60 mg. of pituitary adrenocorticotropic hormone daily until the symptoms have largely or completely disappeared and the sedimentation rate has approached normal. This may take 10 to 20 days. Then smaller maintenance doses should be given for one or two more weeks: about 100 mg. of cortisone or about 30 mg. of pituitary adrenocorticotropic hormone daily. The patient should then be carefully watched for another two weeks or so, and if any signs of rheumatic activity recur (any one or more of the following: rising sedimentation rate; fever; significant increases in resting pulse rate or P-R interval,

16. Polley, H. F., and Mason, H. L.: Rheumatoid Arthritis: Effects of Certain Steroids Other Than Cortisone and of Some Adrenal Cortex Extracts, J. A. M. A. **143**: 1474-1481 (Aug. 26) 1950.

17. (*a*) Edström, G.: Undersökningar över vissa hormoneffekter vid kronisk artrit (ACTH, hypofysinplantation, via adrenalinretning, DOCA, progestin, testosteron), Svenska läkartidningen **46**: 2697-2713 (Dec. 16) 1949; (*b*) Spies, T. D., and Stone, R. E.: Pituitary Adrenocorticotropic Hormone (A. C. T. H.) as a Tool of Clinical and Laboratory Research, Lancet **1**: 11-14 (Jan. 7) 1950. Alexander, W. R. M., and Duthie, J. J. R.: Progesterone in the Treatment of Rheumatoid Arthritis: A Clinical Trial in 5 Cases, ibid. **1**: 297-298 (Feb. 18) 1950. Terry, L. L., and London, F.: Effects of Reichstein's Compound S, Pregnenetriolone Acetate, and 17-Alpha Hydroxyprogesterone in Rheumatoid Arthritis, Proc. Soc. Exper. Biol. & Med. **73**: 251-252 (Feb.) 1950. (*c*) Smith, R. T.: Testosterone, Pregnenolone and Irradiated Ergosterol in Treatment, Philadelphia Med. **45**: 1201-1202 (April 8) 1950. (*d*) Rosenberg, E. F.: Experiences with Compound E (Cortisone), Other Adrenal Cortical Steroids, and Pituitary Adrenocorticotrophic Hormone, Proc. Inst. Med. Chicago **18**: 95-96 (April 15) 1950. Guest, C. M.; Kammerer, W. H.; Cecil, R. L., and Berson, S. A.: Epinephrine, Pregnenolone and Testosterone in the Treatment of Rheumatoid Arthritis, J. A. M. A. **143**: 338-344 (May 27) 1950. Stock, J. P. P., and McClure, E. C.: Pregnenolone in the Treatment of Rheumatoid Arthritis, Lancet **1**: 125-128 (July 22) 1950.

18. Supplied to us by Drs. E. Gifford Upjohn and H. F. Hailman, the Upjohn Company.

19. Freyberg, R. H.; Traeger, C. H.; Adams, C. H.; Kuscu, T.; Wainerdi, H., and Bonomo, I.: Effectiveness of Cortisone Administered Orally, Science **112**: 429 (Oct. 13) 1950. Hench, P. S.; Slocumb, C. H.; Polley, H. F., and Kendall, E. C.: Unpublished data.

20. The combination is advertised in this country as cortilin, as cortinaq and vitamin C or as percorten® with vitamin C.

21. Bilka, P. J.; Hench, P. S.; Slocumb, C. H., and Polley, H. F.: Unpublished data.

22. Thorn and others.[16b] Edström.[17a] Smith.[17c]

or return of articular symptoms) one or the other agent should be given again in fairly generous doses for perhaps 10 to 20 days more. The doses required for children approximate those needed for adults, and the usual pediatric formulas for calculating doses do not fully apply.

In summary, the hormones should be given first in full suppressive doses, then in smaller maintenance doses until it is evident that the underlying acute rheumatic state has disappeared. Consideration should then be given to subsequent prolonged chemoprophylaxis, for example, with penicillin given orally. Because in cases of acute rheumatic fever the hormones need apparently to be given for only a relatively short time, a few weeks, the occurrence of side effects may not provide a significant problem. If minor side effects develop (round face, striae, transient amenorrhea or folliculitis) they can generally be ignored in behalf of the patient's over-all needs. If troublesome edema or other major side effects develop, measures to be mentioned hereafter may suffice to control them.

Rheumatoid Arthritis.—Studies on the development of optimal methods for administering the hormones in the face of chronic rheumatoid arthritis (or other chronic diseases) fall into two groups: the development of (1) a method whereby the results of a relatively short course of hormone administration can be prolonged significantly or (2) a method whereby the hormones can be given more or less continuously without the development of significant side effects.

Optimal After-Effects: As stated previously, about 25 per cent of our rheumatoid patients (first series) obtained pronounced relief which continued (or after a short relapse returned) after the use of the hormones was discontinued. Let us reexamine the methods of administration used in these cases[1] in which after-effects were optimal.

One patient retained relief for only four days after her first eight day course of cortisone (100 mg. daily); after a subsequent 12 day course of pituitary adrenocorticotropic hormone she had a short (four day) relapse and then regained much relief but it lasted only two weeks. After a third (18 day) course of 200 mg. of cortisone daily she retained appreciable relief for seven months.

A second patient was given pituitary adrenocorticotropic hormone for 87 days. Thereafter he has maintained most of his relief to date (nine and a half months).

A third patient was given a long course of cortisone (133 days) after which he had a mild relapse for a month, then regained and maintained almost complete relief for 11 months until influenza precipitated a relapse.

A fourth patient received two long courses of cortisone in suboptimal but progressively effective doses. The first course lasted 75 days; after an interval of 17 days, during which he had a partial relapse, a second course of 140 days was given (total 215 days of cortisone). After this he had a mild relapse, but after 12 months he is still (to date) retaining 80 per cent of the hormonal relief.

A fifth patient who on admission was confined to a wheelchair received cortisone for 25 days, after which she retained most of her decided relief for 14 months.

In summary the excellent after-effects in these five cases followed no one method of administration. In one case they followed a single short course, in another case three short courses in which pituitary adrenocorticotropic hormone alternated with cortisone, and in the three remaining cases one or two fairly long courses. Thus no particular course or method emerges as obviously superior.

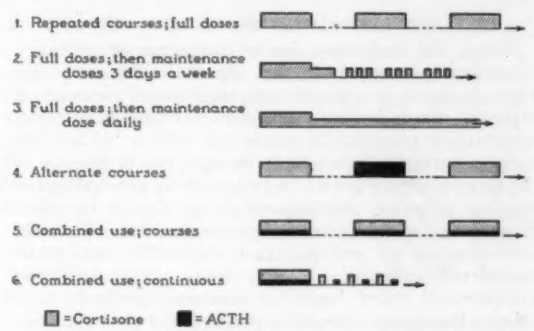
Were these posthormonal remissions spontaneous or related to the use of the hormones? Is 25 per cent the incidence rate of spontaneous remissions which should be expected even in such a group of cases of severe and previously progressive rheumatoid arthritis? Were these patients' symptoms suppressed until a spontaneous remission was due, or were these hormones and the method of their use responsible for the satisfactory after-effects? Further experience must determine the answers to these questions.

METHODS OF ADMINISTRATION UNDER INVESTIGATION

The following methods of administration require further investigation and comparison (see the accompanying illustration):

Repeated Short Courses of Cortisone or Pituitary Adrenocorticotropic Hormone.—Patients so managed would have few if any significant side effects, and the cost would be materially reduced although some relapse should be expected between courses. Whether or not the posthormonal periods of relief would often become successively longer seems uncertain at this time (plan 1 of the illustration).

Alternating Short Courses.—Under this scheme the patient is given a short course of cortisone (until the disease is largely suppressed), then a free interval, then a course of pituitary adrenocorticotropic hormone, another free interval, then more cortisone and so on. The response to such a plan was progressively satisfactory in one case, not unusual in another case. This plan has the advantages and disadvantages of the first plan with an added theoretical advantage: Whatever transient adrenal atrophy and cortical inhibition may result from use of cortisone may be repeatedly neutralized or overcome by the subsequent use of pituitary adrenocorticotropic hormone; in turn the adrenal hypertrophy and hyperplasia induced by the latter agent may be more promptly reduced by the next course of the former (plan 4).


1. Repeated courses; full doses
2. Full doses; then maintenance doses 3 days a week
3. Full doses; then maintenance dose daily
4. Alternate courses
5. Combined use; courses
6. Combined use; continuous
= Cortisone
= ACTH

The optimal method of administration of cortisone or pituitary adrenocorficotropic hormone (ACTH) in the investigative management of chronic diseases such as rheumatoid arthritis has not yet been established. Several different plans of administration are under investigation (see text).

More or Less Continuous Administration of One or the Other Hormone.—Two variants are being studied: (*a*) Some patients have been given full suppressive doses at first and later smaller maintenance doses daily (plan 3). (*b*) Other patients, after the early period of daily suppressive doses, have done well on maintenance doses given only three days a week, for example, on Monday, Wednesday and Friday (plan 2).[2a,c] Larger maintenance doses may be required for this scheme than for the first variant (plan 3).

Other Modifications.—Two other modifications of the three plans of administration thus far investigated are under consideration. These are: repeated short courses of cortisone combined with pituitary adrenocorticotropic hormone and a suppressive course of the combined hormones followed by smaller maintenance doses of each continued indefinitely. These

plans have the supposed advantage of plan 2 plus the theoretical possibility that a more nearly balanced and perhaps more effective cortical secretion might be provided. The value of these last two plans (5 and 6) remains to be proved.

Augmented Administration.—Certain workers have expressed the hope that some substance (gold salts, salicylates, vitamin C or other steroid) might be found which would augment or enhance the effect of doses of cortisone or pituitary adrenocorticotropic hormone which were so small that no side effects would develop. Our experience with salicylates and vitamin C given during courses of these hormones has been disappointing; no potentiation of cortisone was observed.

METHODS OF WITHDRAWAL

Sudden withdrawal of either hormone may be followed by a relatively short period of annoying weakness, occasionally by a "rebound relapse" of articular symptoms. These phenomena are presumably due to the temporary inhibition of adrenal cortex function which use of the exogenous hormones induces. This post-hormonal period of relative adrenocortical insufficiency disappears fairly soon. To minimize it two methods of withdrawal have been suggested: (1) to taper off the daily doses of either of the hormones, giving successively smaller doses the last few (seven to 10) days and (2) to conclude a course of cortisone by giving pituitary adrenocorticotropic hormone for a few days.

PREVENTION AND CONTROL OF SIDE EFFECTS

When the prolonged use of cortisone or pituitary adrenocorticotropic hormone appears necessary (for example, in the investigative management of rheumatoid arthritis) the following procedures will help to prevent, minimize or counteract adverse side effects. When the early suppressive doses have brought the symptoms of the disease largely under control, as soon as possible the smallest effective maintenance doses should be used. Suppression of subjective symptoms, and not necessarily normalization of sedimentation rates also, should be considered sufficient. If the doses needed for full symptomatic relief begin to produce significant side effects, the dosage should be reduced and physician and patient alike should be content with less than full suppression of the disease.

If significant edema develops or persists, a reduced intake of sodium chloride (1 Gm. or less daily for adults) or the oral use of a diuretic such as potassium nitrate (2 Gm. or more three times a day) or both may suffice. For one menopausal woman [1] the administration of estrogen, 5 mg. twice a week, during a second course of cortisone prevented the development of several side effects (among them round face, hypertrichosis and nervousness) which had occurred during the first course. Further studies with estrogen are being made. Significant imbalance of electrolytes will not often occur when the daily doses of cortisone are 100 mg. or less, of pituitary adrenocorticotropic hormone 40 mg. or less, and especially when patients are eating at will rather than having dietary restrictions incident to metabolic studies. If hypopotassemic, hypochloremic alkalosis does occur (with or without muscular weakness, hypertension and electrocardiographic alterations) the oral administration of potassium chloride, 1 or 2 Gm. three times a day, is indicated. Significant nitrogen deficits will probably not develop in the rheumatoid patients who are on unrestricted diets and who are not receiving the larger doses of the hormones. If significant loss of weight and weakness should develop, an increased intake of nitrogen will probably suffice. Testosterone propionate, 25 mg. given intramuscularly daily, in 1 case prevented the nitrogen deficit produced by large doses of cortisone.[5] Testosterone propionate can be given sublingually.

The minor alterations of psyche (grades 1 and 2) need no treatment. The changes described as a grade 3 response may require the establishment of a psychological regimen comparable to that which would be needed to manage the same kind of reaction in other clinical settings. Such adjuncts as sedation, a fixed schedule of activities and the opportunity to discuss basic psychological difficulties can provide a support which may make the continuation of hormonal usage possible. Cessation of hormonal therapy removes the provocative component. Obviously the treatment of the fundamental psychiatric problem needs a special approach. In our experience a frank psychotic response (grade 4) is infrequent and is only likely to occur in patients who are psychologically vulnerable. The hormones should be used with caution for patients with previous history of a psychosis or other evidence of pronounced instability. The management of a hormonally precipitated psychotic episode requires specifically indicated measures to control the response, including the withdrawal of the hormone.[6] Measures to prevent or control postcortisone weakness have been mentioned under "Methods of Withdrawal."

SUMMARY AND CONCLUSIONS

The antirheumatic properties of cortisone and pituitary adrenocorticotropic hormone (ACTH) have been confirmed by several groups of investigators.

During the time of their administration, these hormones have exerted a decidedly suppressive effect on the clinical and biochemical manifestations of rheumatoid arthritis. When the use of the hormones is discontinued symptoms recur rather promptly in most cases, but in several of our cases pronounced improvement has persisted for several (seven to 14) months. The optimal dosage and methods of administration of these hormones for the investigative management of a chronic disease such as rheumatoid arthritis remain to be determined. Several schemes are under investigation. Rather prolonged relief with minimal side effects has been provided in some cases by the continued use of small maintenance doses after the earlier use of larger suppressive doses.

Cortisone or pituitary adrenocorticotropic hormone generally abolishes quickly the manifestations of acute rheumatic fever. There is reason to believe that the lesions of acute rheumatic carditis also are suppressed, in consequence of which the prevention of certain chronic cardiac lesions may be anticipated with some confidence, especially if adequate hormonal usage during the acute rheumatic state is followed by prolonged chemoprophylaxis (for example, with penicillin given orally). The articular complications of disseminated lupus erythematosus and psoriasis are responsive to these hormones. Limited results were obtained in 2 cases of tuberculous arthritis.

These hormones are powerful agents which may affect many functions and tissues of the body besides those of joints and muscles. Their prolonged use, at least in certain doses, may produce certain undesirable effects. These side effects have, to date, been transient and reversible. Certain measures have been developed to minimize or control some of them, but these effects still constitute an important problem for further inves-

tigation. If control of the side effects is not adequate in any given case, smaller doses of the hormones should be used and patient and physician alike should be content with a reduced amount of symptomatic relief.

With the exception of 17-hydroxycorticosterone (compound F of Kendall), none of the currently available steroids chemically related to cortisone appears to have significant antirheumatic properties. The oral administration of one specially prepared extract of adrenal cortex containing compounds E (cortisone) and F produced appreciable relief in 1 case of rheumatoid arthritis and has lent support to the belief that cortisone, and perhaps also compound F, will be chemically effective when given orally.

The mode of action of cortisone and pituitary adrenocorticotropic hormone in rheumatic diseases is not yet known, but the hormones appear to provide to the tissues affected in these diseases a shieldlike buffer against a variety of irritants.

The results of recent and current investigative studies appear to provide justification for the impending restricted application of these hormones to the field of therapy, at least in certain acute rheumatic and articular conditions.

EFFECT OF PITUITARY ADRENOCORTICOTROPIC HORMONE (ACTH) ON RHEUMATIC FEVER AND RHEUMATIC CARDITIS

BENEDICT F. MASSELL, M.D.
and
JOSEPH E. WARREN, M.D.
Boston

That cortisone and pituitary adrenocorticotropic hormone (ACTH) might be useful in the treatment of rheumatic fever was first suggested by Hench and his co-workers [1] in May, 1949, shortly after they had announced their observations on the remarkable effects of these hormones in rheumatoid arthritis.[2] Although more than a year has now elapsed, published data on the effects of these hormones on the clinical course of rheumatic fever are still limited.

Hench's original report [1] included three rheumatic fever patients treated at the Mayo Clinic with cortisone for periods of 21 to 37 days and one patient who had received pituitary adrenocorticotropic hormone for seven days at the time that the report was prepared. More recent publications from the Mayo Clinic [3] have included data on these same cases as well as on four additional cortisone-treated patients and three additional ACTH-treated patients. Elkinton and others [4] administered the latter agent to two patients with rheumatic fever but discontinued the hormone after only three days of treatment. McEwen and his associates [5] reported observations on three patients, one of whom was treated with pituitary adrenocorticotropic hormone alone and two of whom were treated with cortisone first and then with the other hormone. Therapy was continued for periods totaling 30 to 45 days. In a recent article, Thorn and co-workers [6] described the apparent response of a girl with severe rheumatic fever to pituitary adrenocorticotropic hormone administered for a total of only 72 hours.

Preliminary reports of our own experience with this hormone in rheumatic fever have already been published.[7] One of these reports,[7c] which includes detailed case histories of the first 10 patients, covers the period from May 17 to Oct. 23, 1949. During the interval which has elapsed from the latter date to the preparation of this more current report (June 10, 1950), 10 additional patients with definite rheumatic fever [8] have received pituitary adrenocorticotropic hormone therapy at the House of the Good Samaritan. The purpose of the present communication is to summarize our clinical observations on the entire series of 20 patients so treated.

CLINICAL MATERIAL AND METHOD OF TREATMENT

The manifestations of rheumatic fever and carditis present in each of the 20 patients at the time pituitary adrenocorticotropic hormone therapy was begun are indicated in table 1. The duration of the rheumatic attack prior to the beginning of hormone treatment, the number of previous attacks of rheumatic fever, and the age and sex of the patients are summarized in table 2. It is evident from these data that nearly all of the important manifestations of rheumatic fever are represented by this clinical series and that the majority of the patients had severe rheumatic fever and a high degree of active rheumatic carditis.

To obtain information regarding the optimum method of applying pituitary adrenocorticotropic hormone [9] to the treatment of rheumatic fever, various dosage schedules have been tried. These variations in therapy include amount of drug in each individual dose, total daily amount, number of doses per day, number of days of treatment, and total amount administered throughout the period of therapy. In the majority of the patients the total daily dose of the hormone was gradually reduced as treatment progressed, but in some cases the daily amount was kept constant. Some of the more pertinent data relevant to treatment are summarized in table 3.

Read in the Symposium on ACTH and Cortisone before the Section on Experimental Medicine and Therapeutics at the Ninety-Ninth Annual Session of the American Medical Association, San Francisco, June 28, 1950.

From the House of the Good Samaritan (Children's Medical Center). This study was supported by grants from the Helen Hay Whitney Foundation and the National Heart Institute of the United States Public Health Service.

1. Hench, P. S.; Slocumb, C. H.; Barnes, A. R.; Smith, H. L.; Polley, H. F. and Kendall, E. C.: Effects of Adrenal Cortical Hormone 17-Hydroxy-11-Dehydrocorticosterone (Compound E) on Acute Phase of Rheumatic Fever: Preliminary Report, Proc. Staff Meet., Mayo Clin. **24**: 277-297 (May) 1949.

2. Hench, P. S.; Kendall, E. C.; Slocumb, C. H., and Polley, H. F.: Effect of Hormone of Adrenal Cortex (17-Hydroxy-11-Dehydrocorticosterone: Compound E) and of Pituitary Adrenocorticotropic Hormone on Rheumatoid Arthritis: Preliminary Report, Proc. Staff Meet., Mayo Clin. **24**: 181-197 (April) 1949.

3. Barnes, A. R., and Smith, H. L.: The Effects of the Administration of Cortisone and ACTH on Patients with Acute Rheumatic Fever, Mod. Concepts Cardiovas. Dis. **19**: 59-60 (Feb.) 1950. Hench, P. S.; Kendall, E. C.; Slocumb, C. H., and Polley, H. F.: Effects of Cortisone Acetate and Pituitary ACTH on Rheumatoid Arthritis, Rheumatic Fever and Certain Other Conditions: A Study in Clinical Physiology, Arch. Int. Med. **85**: 545-666 (April) 1950.

4. Elkinton, J. R., and others: Effects of Pituitary Adrenocorticotropic Hormone (ACTH) Therapy, J. A. M. A. **141**: 1273-1279 (Dec. 31) 1949.

5. McEwen, C., and others: The Effect of Cortisone and ACTH on Rheumatic Fever, Bull. New York Acad. Med. **26**: 212-228 (April) 1950.

6. Thorn, G. W.; Forsham, P. H.; Frawley, T. F.; Hill, S. R., Jr.; Roche, M.; Staebelin, D., and Wilson, D. L.: The Clinical Usefulness of ACTH and Cortisone, New England J. Med. **242**: 783-793 (May 18) 1950; 824-834 (May 25) 1950; 865-872 (June 1) 1950.

7. (*a*) Massell, B. F.; Warren, J. E., and Sturgis, G. P.: Observations on Effects of ACTH in Patients with Rheumatic Fever and Rheumatic Carditis, in Mote, J. R.: Proceedings of the First Clinical ACTH Conference, Philadelphia, The Blakiston Company, 1950, pp. 405-422. (*b*) Thorn, G. W.; Bayles, T. B.; Massell, B. F.; Forsham, P. H.; Hill, S. R., Jr.; Smith, S, III, and Warren, J. E.: Studies on the Relation of Pituitary-Adrenal Function to Rheumatic Disease, New England J. Med. **241**: 529-537 (Oct. 6) 1949. (*c*) Massell, B. F.; Warren, J. E.; Sturgis, G. P.; Hall, B., and Craige, E.: Clinical Response of Rheumatic Fever and Acute Carditis to ACTH, ibid. **242**: 641-647 (April 27); 692-698 (May 4) 1950.

8. Not included in this group is one patient with possibly complicating bronchiectasis and several patients in whom the clinical course has not sufficiently progressed for adequate evaluation.

9. The pituitary adrenocorticotropic hormone used in these studies was supplied by Dr. John R. Mote of the Armour Laboratories, Chicago. All doses are recorded in terms of milligrams of the Armour standard.

To facilitate the collection of data needed for studies on the mechanism of hormonal influences in rheumatic fever, nearly all of the patients treated with pituitary adrenocorticotropic hormone were placed on a metabolic balance diet containing an average of 0.6 Gm. of sodium per day. In addition to the usual clinical observations, the study has been controlled by a variety of laboratory tests which have been described elsewhere.[7c]

Treatment is still being given to one patient (case 20) and was only recently discontinued in another (case 19). In the remaining 18 cases the period of follow-up since discontinuation of hormonal therapy has varied from seven weeks to 12 months.

therapy. Pericarditis usually became appreciably diminished or disappeared entirely within three to four days of hormonal treatment, but in three patients (cases 5, 9 and 16) nine to 14 days were required for complete subsidence. With regard to the response in case 9, it should be pointed out that after the first five days of therapy exhaustion of our supply of hormone necessitated discontinuing treatment temporarily during the succeeding five days.

In 4 of 5 patients with subcutaneous nodules the lesions became detectably smaller within seven to 10 days of the beginning of therapy and appeared to be totally absent by the end of two to seven weeks of treat-

TABLE 1.—*Manifestations of Rheumatic Fever and Carditis Present in Twenty Patients at Time Pituitary Adrenocorticotropic Hormone Therapy Was Begun*

Manifestations* in Case	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Fever	X	X	X	X	X	X	X	..	X	X	..	X	X	X	X	X	X	..	..	X
Arthritis																				
Subjective	X	X	..	X	..	X	X	..	X	X	..	..	X	..	X	..	X	..	..	..
Objective	..	..	..	X	..	X	X	..	..	X	..	..	..	..	X	..	X	..	..	..
Nodules	X	..	X	..	..	..	..	..	X	..	..	X	X	..	..	..	..	..	..	..
Chorea	..	..	..	..	..	..	..	X	..	..	..	..	..	..	..	..	..	..	X	..
Gallop rhythm	X	X	X	..	..	..	X	..	..	..	..	X	X	..	..	..	..	..	..	..
Pericarditis	X	..	..	..	X	..	X	..	X	..	..	..	..	X	..	X	..	..	..	..
Congestive failure	..	X	X	..	X	..	..	..	..	X	..	..	X	..	..	..	..	X	..	..
Elevated sedimentation rate	X	X	..	X	X	X	X	X	X	X	X	X	..	X	X	X	X	X	..	X
Significant murmurs																				
Mitral systolic	X	X	X	X	X	..	X	X	X	X	X	X	X	X	X	X	X	X	..	X
Mitral diastolic	X	X	X	X	X	..	X	X	X	X	..	..	X	X	X	X	X	X	..	..
Aortic diastolic	X	X	..	..	..	..	X	..	X	X	..	..	..	X	X	..	X	X	..	..

* Letter X indicates presence of manifestation.

TABLE 2.—*Duration of Rheumatic Fever Attack Prior to Pituitary Adrenocorticotropic Hormone Therapy; Number of Previous Attacks; Duration of Rheumatic Fever After Beginning of Therapy and Duration of Follow-Up Since Discontinuation of Hormone*

Case	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Sex	F	F	F	F	F	F	M	M	M	M	F	F	M	F	F	M	M	F	F	F
Age in years	11	21	7	10	8	7	7	7	12	17	13	6	8	12	12	10	8	17	6	12
Number of previous attacks of rheumatic fever	0	6	0	2	0	0	0	0	0	2	0	0	0	1	1	1	1	2	0	0
Duration* of attack prior to therapy	30 D	51 D	80 D	12 D	32 D	7 D	6 D	80 D	54 D	30 D	52 D	150 D	183 D	15 D	31 D	20 D	10 D	3.5 Y	13 D	28 D
Duration* of active rheumatic fever after beginning of therapy																				
Based on clinical signs only	42 D	50 D	170 D	32 D	56 D	2 D	3 D	30 D	49 D	21 D	2 D	30 D	†	4 D	1 D	25 D	3 D	†	†	§
Based on laboratory and clinical signs	65	†	170	53	87	30	51	30	111	106	16	30	†	6	84	67	34	†	†	§
Duration* of follow-up after discontinuation of hormone	11 M	1 Y	11 M	11 M	9 M	11 M	11 M	10 M	8 M	7 M	10 M	8 M	3 D‡	4 M	4 M	3 M	7 W	3 M	8 D	§

* In indicating time D is used for days, W for weeks, M for months and Y for years.
† Indicates that signs of active rheumatic fever did not subside during the period of observation.
‡ This patient died of jugular thrombophlebitis.
§ Still receiving pituitary adrenocorticotropic hormone therapy.

INITIAL RESPONSE OF VARIOUS MANIFESTATIONS

The number of days after the beginning of pituitary adrenocorticotropic hormone therapy for the more important symptoms and signs of rheumatic fever to disappear in each of the 20 patients is indicated in table 4. Attention should be called to the fact that the figures in the table refer to the time for initial disappearance. Certain rheumatic manifestations reappeared in some cases usually when the agent was reduced in dosage or entirely omitted. This aspect of the problem is discussed below more fully. An instance of what is considered to be a good response to pituitary adrenocorticotropic hormone is illustrated by figure 1.

It is evident from the data in table 4 that of all symptoms and signs fever and polyarthritis came under control most rapidly. In most instances these two manifestations subsided within one or two days of ment. In one patient (case 3) the nodules became smaller gradually and did not entirely disappear until about three weeks after termination of therapy. Furthermore, new nodules appeared shortly afterward on both forearms distal to the olecranon processes.

The erythrocyte sedimentation rate usually became significantly slower after one to five days of treatment and in the majority of patients reached a normal level within one to three weeks. In 4 patients (cases 5, 7, 15 and 17) the response was slower, and one to three months of therapy elapsed before normal readings were observed.

Only 2 of the patients in this series (cases 8 and 19) had chorea. In the first of these improvement during therapy was quite striking. Although the hormone was given for a total of only 10 days, at the end of this period the chorea, which had been moderately severe

prior to treatment, had become mild. Thereafter and without further therapy the slight residual chorea gradually lessened and within another three weeks completely disappeared. The second patient, recently admitted to the hospital, had moderately severe chorea of nearly one month's duration. After 10 days of therapy with relatively large doses of the hormone, the chorea was no less severe than it had been before this treatment; therefore, in order to determine whether withdrawal of the hormone would have any influence on the choreiform motions, treatment was discontinued. It is too soon to evaluate the effect of this procedure.

Improvement in appetite and gain in weight with pituitary adrenocorticotropic hormone therapy was frequently impressive and was often remarkably prompt. Disappearance of moderate anemia in association with other signs of improvement was likewise noticeable in a number of cases. In several patients who had a decided sinus tachycardia there was considerable slowing of the heart rate soon after treatment was begun. In addition the hormone may also have played a role in the improvement of one patient with paroxysmal auricular tachycardia (case 11).

The influence of pituitary adrenocorticotropic hormone on congestive heart failure was somewhat variable; therefore it can best be described by considering separately each of the 6 patients in whom this manifestation of active carditis was present.

CASE 2.—A woman aged 21 had severe heart damage as the result of long-standing repetitive rheumatic fever. She had been on a maintenance dose of digitalis for some time. With her most recent rheumatic recurrence there developed severe congestion of the liver and sacral edema which failed to respond to a low sodium diet and frequent administration of a mercurial diuretic. During the first week of pituitary adrenocorticotropic hormone therapy the signs of congestion lessened slightly. Then, with temporary omission of hormone therapy for a period of three days (due to exhaustion of our supply) there was a decided diuresis accompanied with further striking improvement in the signs of congestive failure. When hormone therapy was resumed a satisfactory urinary output was maintained, and improvement continued so that by the fourteenth day after the initial dose of pituitary adrenocorticotropic hormone signs of congestive failure could not longer be detected. Thereafter the patient was able to get along well without the further administration of diuretics. Some of the pertinent features of this patient's clinical response to the hormone, including the urinary excretion of sodium, are illustrated in figure 2.

TABLE 3.—*Pertinent Data Regarding Pituitary Adrenocorticotropic Hormone Dosage*

Case	1	2	3	4	5	6	7	8	9	10
Weight in Kg.	25.9	46.3	25.0	27.2	21.3	31.0	19.7	22.9	29.9	54.0
Type of treatment*	R	R	R	R	R	R	R	C	R	R
Entire period of therapy:										
Total days	52	39	40	46	160	31	31	11	68	49
Total amount in mg.	970	1,228	566	572	1,511	306	348	310	2,370	1,560
Average daily amount in mg.	18.6	31.5	14.2	12.4	15.1	9.9	11.2	28.3	34.8	31.8
Average daily amount in mg./Kg.	0.7	0.7	0.6	0.4	0.7	0.3	0.6	1.2	1.2	0.6
Initial period of therapy (before reduction in dosage):										
No. of days	4	3	11	10	3	3	3	11	4	3
No. of doses/day	4	4	4	4	4	4	4	3	4	3
No. of mg./dose	9.0	9.0	7.5	7.5	12.5	7.5	7.5	10.0	20.0	20.0
Total daily amount in mg.	36	36	30	30	50	30	30	30	80	60
Total daily amount in mg./Kg.	1.4	0.8	1.2	1.1	2.3	1.0	1.5	1.3	2.7	1.1

Case	11	12	13	14	15	16	17	18	19	20
Weight in Kg.	45.6	22.5	22.0	38.1	40.8	37.7	25.6	49.0	22.5	19.0
Type of treatment*	C	C	R	R	C	R	C	R	C	C
Entire period of therapy:										
Total days	4	27	81	33	35	37	37	51	10	28†
Total amount in mg.	190	1,050	1,079	494	320	709	358	1,530	540	280
Average daily amount in mg.	47.5	38.9	13.3	15.0	14.6	18.9	9.7	29.8	54.0	10.0
Average daily amount in mg./Kg.	1.0	1.7	0.6	0.4	0.4	0.5	0.4	0.6	2.4	0.5
Initial period of therapy (before reduction in dosage):										
No. of days	3	26	7	11	33	14	36	10	8	28†
No. of doses/day	4	4	4	3	3	3	3	3	4	3
No. of mg./dose	10.0	10.0	6.3	8.3	5.0	10.0	3.3	10.0	15.0	3.3
Total daily amount in mg.	40	40	25	25	15	30	10	30	60	10
Total daily amount in mg./Kg.	0.9	1.8	1.1	0.7	0.4	0.8	0.4	0.6	2.7	0.5

* C indicates constant daily amount of pituitary adrenocorticotropic hormone during period of therapy; R indicates daily amount gradually reduced during period of therapy.
† Treatment not yet discontinued.

TABLE 4.—*Days After Beginning of Therapy Required for First Subsidence of Manifestations of Rheumatic Fever* *

Manifestations in Case	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Fever	1	1	..	1	2	1	1	..	1	1	..	..	..	1	1	1	1	..	..	1
Arthralgia	1	1	..	1	..	2	1	..	4	1	..	..	1	..	1	..	1	..	..	..
Objective arthritis	..	..	..	2	..	2	1	..	..	3	..	..	..	..	1	..	1	..	..	..
Pericardial friction rub	3	..	..	..	11	..	1	..	14	..	..	..	..	4	..	9	..	..	..	..
Nodules	45	..	†	..	..	..	..	..	30	..	..	20	14	..	..	..	..	..	..	..
Elevated sedimentation rate	17	22	..	20	87	15	34	6	17	5	16	11	..	6	50	56	10	..	..	†
Congestive failure	..	14	†	..	56	..	..	..	..	15	..	..	†	..	..	..	..	†	..	..
Chorea	..	..	..	..	..	..	..	30	..	..	..	..	..	..	..	..	..	..	†	..

* Figures refer to the number of days required for initial disappearance of manifestations; certain of these reappeared later. Instances in which subsidence of manifestation was not clearly associated with therapy are omitted.
† Manifestation did not completely subside during the period of observation.

Case 3.—A girl 7 years of age had severe rheumatic carditis and congestive failure, the latter condition being indicated by the presence of a gallop rhythm, an enlarged tender liver, cough and orthopnea. Prior to the administration of pituitary adrenocorticotropic hormone the patient had been on a low sodium diet but had not received other cardiac therapy. During the first three days of hormone treatment the signs of congestion of the liver and lungs increased to such an extent that a daily mer-

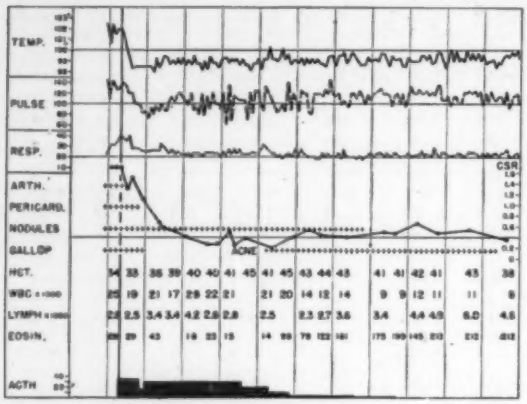


Fig. 1 (case 1).—Chart showing clinical response of patient to pituitary adrenocorticotropic hormone (ACTH) therapy. Light vertical lines indicate weekly intervals. The heavy vertical line indicates the beginning of therapy. Note transient rise in sedimentation rate when the hormone was reduced to low dosage. In column at left HCT indicates the hematocrit level.

curial diuretic was added to the therapeutic regimen. Thereafter the signs of congestion lessened considerably, so that three weeks after the beginning of hormone treatment the only residual sign possibly indicative of congestive failure was a liver edge palpable just slightly below the costal margin. Furthermore, administration of the mercurial diuretic was omitted two weeks later without the development of any increase in the signs of congestion.

Case 5.—A girl 8 years of age had severe rheumatic carditis and pronounced congestion of the liver. In spite of a low sodium diet the first four days of pituitary adrenocorticotropic hormone therapy were accompanied with an increase in hepatic congestion and a decided increase in the respiratory rate. With the daily administration of a mercurial diuretic the signs of congestive failure regressed, and one month after the first injection of the hormone the patient was sufficiently improved to allow discontinuation of diuretic therapy. Although slight liver enlargement persisted, there was no doubt that the signs of congestion were considerably improved in comparison to those present prior to hormone treatment.

Case 10.—A boy aged 17 had severe active rheumatic fever, long-standing rheumatic heart disease and auricular fibrillation. Prior to pituitary adrenocorticotropic hormone therapy, in spite of full digitalization, he was in severe congestive failure with hepatic enlargement. Digitalis was withheld, and on the sixth hospital day hormone therapy was begun. By the eighteenth hospital day (twelfth day of the hormone) the heart rate had increased to 150 beats per minute; the liver had become larger and was quite tender; there was slight sacral edema, and the patient was obviously orthopneic. Consequently the patient was rapidly redigitalized by the intravenous route with crystalline lanatoside C. This therapeutic procedure was followed by a prompt slowing of the heart rate and a rapid disappearance of all signs of congestion. Furthermore, with a maintenance oral dose of digitoxin the heart rate remained well controlled and there was no recurrence of congestive failure.

Case 13.—A boy 8 years of age had active rheumatic fever of six months' duration and chronic hepatic congestion of at least three and one half months' duration. With pituitary adrenocorticotropic hormone and diuretic therapy the size of his liver diminished somewhat but nevertheless continued to remain obviously enlarged. Furthermore, the patient finally died after three months of hormone treatment as the result of bilateral thrombophlebitis of the internal jugular vein, and autopsy revealed the presence of chronic passive congestion of the liver.

Case 18.—A girl aged 17 had smoldering active rheumatic fever which had persisted ever since her third frank attack of acute rheumatic fever three and one half years previously. Increasing sinus tachycardia, development of frequent attacks of paroxysmal auricular tachycardia and enlargement of the liver gave evidence of progressive cardiac damage. With pituitary adrenocorticotropic hormone therapy the signs of hepatic congestion increased, but the situation was reasonably well controlled by the use of diuretics and a low sodium diet. After the discontinuation of hormone therapy, even though a low sodium diet and frequent administration of diuretics were continued, definite signs of hepatic congestion persisted.

The final rheumatic manifestation to be considered is the auscultatory signs of heart disease. Such signs were present in 18 of the 20 patients in this series. In most instances the significant murmurs were due to long-standing valvular damage, and, as might be expected, they were not influenced by pituitary adrenocorticotropic hormone therapy. But in 5 cases significant murmurs, which presumably were of relatively recent origin, regressed in association with other clinical signs of improvement and finally disappeared completely within several weeks to several months. The auscultatory signs which disappeared included a moderately loud mitral systolic murmur in one instance, mitral middiastolic murmurs in three instances and faint to moderately intense aortic diastolic murmurs in four instances. In spite of the disappearance of some murmurs, other murmurs have given ample evidence of persistent heart disease in three of the five patients (cases 4, 14 and 15). However, two of the five patients (cases 1 and 7), during a follow-up period of about 11 months, have remained entirely free of signs of residual cardiac damage.

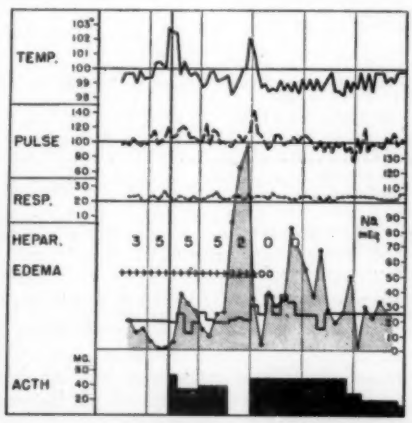


Fig. 2 (case 2).—Chart showing effect of pituitary adrenocorticotropic hormone in a patient with congestive failure. The patient was on a constant regimen of digitoxin 0.1 mg. and a mercurial diuretic 1 cc. per day. Light vertical lines indicate weekly intervals. The heavy vertical line indicates the beginning of therapy. The shaded area indicates urinary excretion of sodium in milliequivalents per day. The heavy line through the shaded area indicates sodium intake per day. Note the rise in temperature and the decided sodium diuresis when the hormone was temporarily discontinued after eight days of therapy.

WITHDRAWAL EFFECTS

When pituitary adrenocorticotropic hormone was withdrawn abruptly early in the course of treatment of patients with acute rheumatic fever an almost immediate rise in temperature and return of symptoms occurred, a result that was not surprising. Of possibly

greater significance was the reaction to gradual reduction in dosage and final omission of therapy. In some instances the procedure was not associated with any untoward effect. In others, however, relapses of varying severity were observed. The interesting feature of these late withdrawal reactions is that in a number of instances fever, joint pains and rise in sedimentation rate again subsided and failed to reappear even though the reduced hormone dosage was kept constant or the hormone was omitted altogether. As might be expected, elevation of the sedimentation rate subsided more slowly than did the clinical manifestations of these withdrawal reactions. In general, clinical withdrawal symptoms lasted for only three to 10 days, but rebound elevation of the sedimentation rate did not subside entirely for periods varying from one week to three months. A withdrawal reaction involving only the sedimentation rate is illustrated in figure 1.

The effect of withdrawing pituitary adrenocorticotropic hormone in one patient (case 18) is of especial interest and worthy of further consideration. This patient is the girl aged 17 to whom reference has already been made in connection with the effect of the hormone on congestive heart failure. She had had persistent smoldering active rheumatic fever for about three and one half years prior to therapy, but during this period she did not have any fever. When after seven weeks of treatment the dose was reduced to 10 mg. per day and a little later omitted entirely, fever developed with the patient's oral temperatures reaching as high as 103.5 F. During the next 10 weeks fever persisted except for varying intervals when the patient was treated with aspirin (acetylsalicylic acid), ascorbic acid in large doses or more pituitary adrenocorticotropic hormone. All antirheumatic therapy was finally omitted a little over two weeks ago, and so far the temperature has remained normal. A careful search has been made for possible causes for the fever, unrelated to rheumatic fever, but so far none has been found; therefore it seems quite possible, in spite of the lack of other obviously rheumatic manifestations, that the febrile withdrawal reaction in this patient represents a recrudescence of rheumatic fever.

UNTOWARD REACTIONS

From the previous discussion of the effect of pituitary adrenocorticotropic hormone on congestive heart failure it is evident that in a number of instances this condition was aggravated during the early period of hormone therapy. The tendency of the drug to cause water retention may in turn be due to its sodium-retaining effect or in part to a direct effect on the kidneys of contaminating antidiuretic principles in the hormonal preparation. Whatever the cause, the effect constitutes a distinct risk for the patient with severe carditis. Fortunately in our patients aggravation of congestive failure was adequately controlled by the use of diuretics and a diet exceedingly low in sodium.

The only other serious untoward reaction which can be reasonably attributed to pituitary adrenocorticotropic hormone therapy in this series of 20 patients is a single instance of severe mental depression. This latter condition developed in a woman aged 21 (case 2) after treatment for about one month but disappeared again one month after discontinuation of hormone treatment.

One patient with severe active carditis and chronic congestive failure (case 13) was treated with the hormone in gradually reduced dosage for about three months. Toward the end of this period, while he was receiving only 4 mg. per day, there developed bilateral thrombophlebitis of the internal jugular veins and he died shortly thereafter. Although the possibility must be considered that the hormone may have played a role in the development of this fatal complication, other contributory factors to be considered are active rheumatic fever, congestive failure with venous stasis and the mercurial diuretic which was administered frequently in an attempt to combat the congestive failure.

Other relatively minor side effects from pituitary adrenocorticotropic hormone were transient headache in two cases, slight striae in two cases, acne in seven cases and development of varying degrees of roundness of the face in eight cases. The latter two manifestations usually became apparent during the second to fourth week of treatment and lessened gradually after discontinuation of therapy. In eight patients there developed no side reactions whatsoever. Significant elevation of the blood sugar level, glycosuria and hypertension were not observed in any of the 20 patients of this series.

THERAPEUTIC WORTH OF THE HORMONE

The prompt reduction in fever, the rapid disappearance of joint symptoms and the other immediate effects of pituitary adrenocorticotropic hormone therapy (indicated in table 4) which have already been discussed are extremely impressive. It must be pointed out, however, that the assessment of antirheumatic agents should not be based on immediate effects alone. If a drug is to have real value in the treatment of rheumatic fever it must do one or more of the following things: (1) shorten the course of the attack of rheumatic fever; (2) suppress active carditis, and (3) prevent or reduce residual cardiac damage.

Data relative to duration of the observed attacks of rheumatic fever in the first 19 patients of this series in whom hormone therapy has been completed are presented in table 2. The attacks were not considered to have been terminated until the effects of the withdrawal reactions, in those cases in which such reactions occurred, also subsided. Duration of active rheumatic fever is recorded in the table in two ways: (1) duration of clinical manifestations without regard to laboratory observations, and (2) total duration of rheumatic activity based on both clinical and laboratory results, especially the erythrocyte sedimentation rate.

One patient (case 19) with moderately severe chorea failed to show any improvement after ten days of therapy with large doses of pituitary adrenocorticotropic hormone. Another patient (case 13) died of a complicating jugular thrombophlebitis after about three months of therapy. A third patient (case 18) with previous persistent low grade rheumatic fever has continued to have active rheumatic fever in spite of therapy. As has already been indicated in a previous discussion, it is even possible in this case that the rheumatic process has actually increased in severity since discontinuation of the course of pituitary adrenocorticotropic hormone. A fourth patient (case 3), although finally recovered from rheumatic fever, must be considered a therapeutic failure because she did not seem to improve during the period of hormone treatment.

Of the remaining 15 patients final clinical recovery was observed in five patients within only one week of hormone therapy, in six patients within two to four weeks after the beginning of treatment and in four patients not until six to eight weeks after the first injection of the hormone. If the analysis is done on the basis of laboratory tests, particularly the erythrocyte

sedimentation rate, as well as clinical manifestations, the time which elapsed between the initial dose of pituitary adrenocorticotropic hormone and apparent complete recovery was one to two weeks in two patients, four weeks in four patients, one to two months in four patients, and two to four months in four patients.

One patient (case 2), the woman aged 21 to whom reference has been previously made, was observed in her seventh attack of rheumatic fever and was treated with the hormone after she had been extremely ill for about seven weeks. Her sedimentation rate had been observed frequently to be slightly elevated prior to the onset of the last rheumatic recurrence. The patient made an excellent initial response to therapy, and all clinical manifestations completely subsided about seven weeks after she received the first dose of the hormone. However, during a 12 month follow-up since completion of treatment her sedimentation rate has continued at a slightly elevated level, a level comparable to that which had been present prior to her last recurrence of rheumatic fever.

Returning now to the question whether or not pituitary adrenocorticotropic hormone shortened the course of the rheumatic fever attacks, it is our impression from the data presented here that, in spite of obvious therapeutic failure in four instances, the duration of the rheumatic process in many of the patients was considerably less than it would have been without therapy. This impression is particularly strong when we assess the course of the hormone-treated patients in the light of our previous experience at the House of the Good Samaritan with patients whose illnesses have been of comparable severity. Nevertheless, it should be emphasized that it is strictly an impression. The well known variability of rheumatic fever even when it is uninfluenced by therapy, the variable course of the disease in the patients treated with pituitary adrenocorticotropic hormone and the relatively small number of patients so treated necessitate postponement of final judgment until there has been an opportunity to observe the effect of the hormone on a large number of patients with rheumatic fever and to compare the clinical course of these patients with that of an adequate group of controls.[10]

In regard to the second criterion of antirheumatic activity, namely, the suppression of active carditis, final judgment must also be postponed until our experience has been more extensive. Nevertheless there are indications from our data that active carditis was actually suppressed by pituitary adrenocorticotropic hormone in at least some of the patients. These indications are as follows:

1. *Rapid Disappearance of Signs of Pericarditis.*—This phenomenon was observed in six patients (see table 4).

2. *Regression and Disappearance of Significant Murmurs.*—These changes were observed in five early cases.

3. *Effect on Congestive Heart Failure.*—The fluid-retaining effect of pituitary adrenocorticotropic hormone and the consequent risk of increasing congestive failure, especially early in the course of treatment, has already been discussed. Nevertheless, the severity of congestive failure in four of the six patients with this manifestation was notably diminished after two to four weeks of hormone treatment. Since active carditis plays a primary role in the production of congestive failure in young rheumatic fever patients, it is reasonable to believe that the observed improvement in congestive manifestations reflected a reduction in the severity of carditis.

4. *Effect on Subcutaneous Nodules.*—The apparent suppression by pituitary adrenocorticotropic hormone of this proliferative rheumatic lesion in four patients suggests that the hormone may have a similar effect on the myocardial lesions which in microscopic architecture often closely resemble subcutaneous nodules.

5. *Necropsy Observations in One Patient Who Died of Jugular Thrombophlebitis.*—Microscopic examination of the myocardium and endocardium revealed areas consistent with a subacute or healing process, but Aschoff bodies were not observed and fibrinoid changes were minimal.

The third and final criterion to be considered in the assessment of pituitary adrenocorticotropic hormone is whether it reduces or prevents residual heart damage. In many respects this effect is intimately related to the effect on active carditis because it seems reasonable to believe that if the inflammatory process in the heart can be suppressed residual damage to the heart can also be prevented or at least reduced. Therefore such observations as those outlined in connection with the problem of carditis lead us to hope that the hormone may also prevent heart damage, especially if treatment can be instituted early.

Among the first 18 patients, all of whom we had the opportunity to observe for one month or longer after the discontinuation of hormone therapy, there was only one patient (case 6) in whom significant murmurs were not heard during the acute attack. In two other patients (cases 1 and 7) obviously significant murmurs heard early in the course of the illness subsequently disappeared. All three patients have continued to have apparently normal hearts during a follow-up period of 11 months. However, in view of the occasional insidious development of valvular disease several years after an original attack of rheumatic fever, a considerably longer period of follow-up study will be necessary before we can be assured that the hearts of these three patients have escaped damage. Furthermore, final assessment of pituitary adrenocorticotropic hormone therapy in regard to the prevention of residual heart damage will require observations of many additional early cases and a careful follow-up study of such cases.

In general, then, final conclusions are not yet warranted with regard to the therapeutic worth of pituitary adrenocorticotropic hormone as an antirheumatic agent. Nevertheless, there are strongly suggestive indications that in some cases the hormone may be effective in shortening the course of rheumatic fever attacks and in suppressing active carditis. There is also reason to be hopeful that such therapy when given early in an attack of rheumatic fever may prevent or decrease residual heart damage.

From our limited data we have not been able to correlate the results of treatment with the dosage of the hormone. There are suggestive indications, however, that there may be some correlation of results with the duration of the rheumatic process when pituitary adrenocorticotropic hormone therapy is begun. We have the impression that early acute attacks of the disease may be more readily controlled than attacks which have already been in progress for many months before treatment is instituted.[11]

MECHANISM OF HORMONAL INFLUENCES IN RHEUMATIC FEVER

It seems quite likely that the influence of pituitary adrenocorticotropic hormone in rheumatic fever is indirect and depends on stimulation of the adrenal cortex

10. The difficulty of obtaining an adequate group of untreated controls should be recognized.

11. McEwen and his associates [8] also gained a similar impression from their studies.

and a consequent increased endogenous production of 11,17-oxysteroids, but the way in which the adrenocortical steroids in turn suppress the inflammatory rheumatic process is still not understood.

Pituitary adrenocorticotropic hormone and cortisone have a number of interesting physiological effects.[6] These include: alterations in the metabolism of electrolytes, water, carbohydrates, fats and proteins; depression of the level of circulating eosinophils in the blood, and, at least in patients with active rheumatic fever, a decided reduction in the serum concentration of gamma globulin and in the titer of antistreptolysin O.[7,8] In view of the presence of a high concentration of ascorbic acid in the adrenal cortex and the reduction of ascorbic acid content when the adrenal cortex is stimulated by pituitary adrenocorticotropic hormone,[12] a recent study [13] indicating that ascorbic acid possesses some antirheumatic activity when administered by mouth in large doses is also of interest. However, it is not known whether the observations on the physiological changes induced by hormones or the observations on ascorbic acid have any real significance in relation to the problem of the therapeutic mechanism of pituitary adrenocorticotropic hormone and cortisone in rheumatic fever.

SUMMARY AND CONCLUSIONS

The clinical effect of pituitary adrenocorticotropic hormone (ACTH) has been observed in 20 patients with active rheumatic fever. In many patients the rheumatic process was severe, and most of them had active carditis.

The initial response of fever and joint involvement was especially impressive, but pericarditis, subcutaneous nodules and other rheumatic manifestations also frequently disappeared during hormone therapy.

Withdrawal reactions with clinical manifestations of rheumatic fever or with only elevation of the sedimentation rate were sometimes observed when hormone therapy was completed. In most but not all such instances these signs of rheumatic activity again subsided spontaneously over varying periods of time without any further treatment.

Of two patients with chorea, one showed striking improvement in association with pituitary adrenocorticotropic hormone therapy; the other failed to respond to a 10 day period of treatment with the hormone in large doses.

Treatment has been completed in 17 of the 18 patients with rheumatic manifestations other than chorea. Three of these cases must be considered therapeutic failures. Although the total duration of active rheumatic fever varied greatly in the remaining 14 patients, it was our impression that, on the whole, recovery took place sooner than it would have without treatment.

The apparent response of pericarditis, congestive failure and subcutaneous nodules to pituitary adrenocorticotropic hormone in a number of patients and the complete disappearance in two patients of all significant murmurs strongly suggest that in some instances active carditis may be favorably influenced by hormone treatment. Also, there are hopeful indications that if therapy is begun early in an attack of rheumatic fever cardiac damage may be lessened or prevented.

The only harmful reactions definitely attributable to pituitary adrenocorticotropic hormone in this series were retention of fluids with aggravation of congestive heart failure and, in one instance, serious mental depression. It is possible that in one patient with long-standing low grade rheumatic fever the degree of rheumatic activity was greater after discontinuation than prior to the administration of the hormone. One instance of fatal jugular thrombophlebitis was encountered, but as yet there is no definite reason to attribute this complication to pituitary adrenocorticotropic hormone therapy.

The mechanism of hormonal influences in rheumatic fever is not yet understood.

12. Sayers, G., and Sayers, M. A.: Pituitary-Adrenal System, Ann. New York Acad. Sc. **50**: 522-539 (June 27) 1949.

13. Massell, B. F.; Warren, J. E.; Patterson, P. R., and Lehmus, H. J.: Antirheumatic Activity of Ascorbic Acid in Large Doses: Preliminary Observations on 7 Patients with Rheumatic Fever, New England J. Med. **242**: 614-615 (April 20) 1950.

PHYSIOLOGICAL EFFECTS OF CORTISONE AND PITUITARY ADRENOCORTICOTROPIC HORMONE (ACTH) IN MAN

RANDALL G. SPRAGUE, M.D.
MARSCHELLE H. POWER, Ph.D.
and
HAROLD L. MASON, Ph.D.
Rochester, Minn.

Clinical and metabolic studies by us and others before and particularly since the initial observations of Hench, Kendall, Slocumb and Polley [1] have provided evidence that cortisone and pituitary adrenocorticotropic hormone (ACTH) are powerful hormonal substances. It is probable that most, if not all, tissues of the body come within the scope of their activity. When administered to man they are capable of inducing a number of physiologic and pharmacologic alterations in addition to those involved in their favorable effects on a variety of disease states. In some circumstances there may be no distinct line of demarcation between favorable therapeutic effects and other physiological effects, some of them undesirable.

In most of the clinical conditions which have been favorably influenced by administration of these hormones there is no clear evidence of hormonal deficiency. (Exceptions are conditions of frank adrenal cortical insufficiency, such as occur primarily in Addison's disease and secondarily in panhypopituitarism.) Consequently, it appears that in many of these conditions a state of hormonal excess must be created in order to achieve therapeutic benefit. If this state is of sufficient degree and duration a variety of physiological effects, desirable and undesirable, may become manifest.

For the foregoing reasons a thorough understanding of the physiological potentialities of cortisone and pituitary adrenocorticotropic hormone is essential for their safe and effective therapeutic use, particularly in conditions requiring large doses or prolonged administration. In this presentation we shall consider briefly the physiological activity of these agents, as observed in human subjects, under four headings: (1) effects on

From the Division of Medicine, Mayo Clinic (Dr. Sprague) and the Division of Biochemistry, Mayo Foundation (Drs. Power and Mason).

Read in a Symposium on ACTH and Cortisone before the Section on Experimental Medicine and Therapeutics at the Ninety-Ninth Annual Session of the American Medical Association, San Francisco, June 28, 1950.

We are indebted to Merck & Co., Inc., James M. Carlisle, M.D., Medical Director, for the supplies of cortisone, and to Armour and Company, John R. Mote, M.D., Director of Medical Research, for the supplies of ACTH used in these studies.

1. Hench, P. S.; Kendall, E. C.; Slocumb, C. H., and Polley, H. F.: The Effect of a Hormone of the Adrenal Cortex (17-Hydroxy-11-Dehydrocorticosterone: Compound E) and of Pituitary Adrenocorticotropic Hormone on Rheumatoid Arthritis: Preliminary Report, Proc. Staff Meet., Mayo Clin. **24**: 181-197 (April 13) 1949.

metabolism of carbohydrate, protein and fat; (2) effects on metabolism of water and electrolytes; (3) effects on structure and function of the adrenal cortices, and (4) several miscellaneous hormonal effects. It is recognized that not all of the known physiological activities of these hormones are included under these headings.

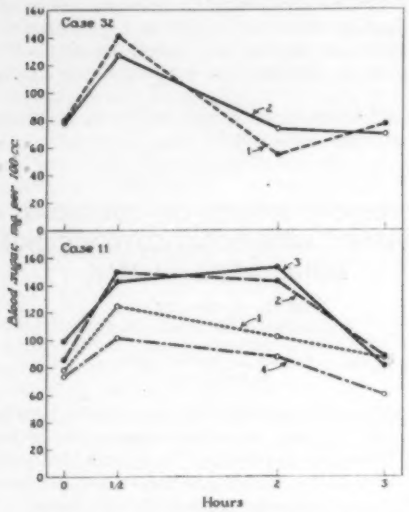


Fig. 1.—Upper (case 32): (1) Normal glucose tolerance in a woman aged 32, with disseminated lupus erythematosus, after administration of cortisone (average 112 mg. daily) for 96 days. (2) Normal glucose tolerance after administration of cortisone (average 107 mg. daily) for 160 days. Lower (case 11): (1) Normal glucose tolerance in a woman aged 40, with rheumatoid arthritis, before administration of cortisone. (2) Impaired glucose tolerance after administration of cortisone for 7 days (average 129 mg. daily). (3) Impaired glucose tolerance after administration of cortisone, in another course, for 16 days (200 mg. daily). (4) Normal glucose tolerance 18 days after withdrawal of cortisone (reproduced from Sprague and others [4]).

EFFECTS ON METABOLISM OF CARBOHYDRATE, PROTEIN AND FAT

Carbohydrate.—That the administration of cortisone or pituitary adrenocorticotropic hormone to man might cause impairment of tolerance for carbohydrate is suggested by several earlier experimental and clinical observations: (*a*) these hormones are capable of inducing hyperglycemia and glycosuria in rats;[2] (*b*) cortisone corrects the abnormal sensitivity to insulin and the tendency to hypoglycemia exhibited by some patients with Addison's disease,[3] and (*c*) impairment of carbohydrate tolerance is a common feature of Cushing's syndrome and is apparently directly related to overproduction of cortisone-like adrenal steroids by hyperfunctioning adrenal cortices in this condition.[3b]

Inasmuch as the doses usually administered to patients are small, relative to body weight, compared to those necessary for the induction of diabetes in animals, it would be anticipated that impairment of carbohydrate tolerance in human subjects receiving these hormones would be slight or absent. In our experience this has generally proved to be the case. Although slight increases in the level of the fasting blood sugar have been observed in some patients during administration of cortisone or pituitary adrenocorticotropic hormone, the values have not usually exceeded the normal range, and more than traces of sugar in the urine seldom have been observed. Among a group of patients receiving cortisone, there was no significant change in the mean value of the fasting blood sugar during or after administration of the hormone as compared to the mean value before its administration (table 1).[4]

Glucose tolerance tests have revealed a significant incidence of slight impairment of carbohydrate tolerance under the influence of cortisone. Among 12 patients, abnormal glucose tolerance curves, presumably due to cortisone, were observed in 4. It is of interest, and possibly of significance, that in 2 of these cases there was a family history of diabetes. In 2 of the 4 patients in whom impairment of glucose tolerance developed during administration of cortisone, tests which were performed after administration of the hormone had been stopped gave normal results.

In some instances no impairment of glucose tolerance was demonstrable after prolonged administration of cortisone. For example, in case 32 (fig. 1, upper) impairment could not be demonstrated after daily administration of the hormone for ninety-six days; after daily administration for 160 days, the glucose tolerance was still normal. In case 11 (fig. 1, lower) the glucose tolerance, which had been normal before administration of the hormone, was abnormal on one occasion after only seven days' administration at an average dose of 129 mg. daily and on another occasion after administration of 200 mg. daily for 16 days. Eighteen days after withdrawal of cortisone the glucose tolerance was again normal.[4]

TABLE 1.—*Changes in Level of the Fasting Blood Sugar During and After Administration of Cortisone*

Mean Value Before Administration, Mg. per 100 Cc.	During Administration		After Administration	
	Cases	Mean Difference, Mg. per 100 Cc.	Cases	Mean Difference, Mg. per 100 Cc.
81.9.....	18	-1.5 ± 1.7 *	16	-2.2 ± 2.0 *

* A minus sign indicates a decrease as compared with the level before administration of cortisone. The figure following the plus and minus sign is the standard error of the mean difference. The mean difference is considered statistically significant if it is twice its standard error. Therefore, neither of the changes tabulated above is considered statistically significant.

In contrast to this relatively benign experience with respect to impairment of carbohydrate tolerance, there have now been several cases observed elsewhere, and one at the Mayo Clinic, in which a temporary state of frank diabetes was induced by either cortisone or pituitary adrenocorticotropic hormone. In the clinic case a boy aged 4 years was found to have glycosuria and a fasting blood sugar level of 171 mg. per 100 cc. after administration of 550 mg. of pituitary adreno-

2. Ingle, D. J.: The Production of Glycosuria in the Normal Rat by Means of 17-Hydroxy-11-Dehydrocorticosterone, Endocrinology **39**: 649-652 (Oct.) 1941. Ingle, D. J.; Li, C. H., and Evans, H. M.: Effect of Adrenocorticotrophic Hormone on Urinary Excretion of Sodium, Chloride, Potassium, Nitrogen and Glucose in Normal Rats, ibid. **39**: 32-42 (July) 1946.

3. (*a*) Thorn, G. W.; Koepf, G. F.; Lewis, R. A., and Olsen, E. F.: Carbohydrate Metabolism in Addison's Disease, J. Clin. Investigation **19**: 813-832 (Nov.) 1940. Sprague, R. G.; Gastineau, C. F.; Mason, H. L., and Power, M. H.: Effects of Synthetic 11-Dehydrocorticosterone (Compound A) in a Subject with Addison's Disease, Am. J. Med. **4**: 175-185 (Feb.) 1948. (*b*) Sprague, R. G.; Mason, H. L., and Power, M. H.: Studies of the Effects of Adrenal Cortical Hormones on Carbohydrate Metabolism in Human Subjects, Proc. Am. Diabetes A. (1949) **9**: 147-166, 1949. (*c*) Thorn, G. W., and Forsham, P. H.: Metabolic Changes in Man Following Adrenal and Pituitary Hormone Administration, Recent Progr. Hormone Research **4**: 229-288, 1949. Sprague, R. G.; Power, M. H.; Mason, H. L., and Cluxton, H. E.: Metabolic Effects of Synthetic Compound E (17-Hydroxy-11-Dehydrocorticosterone) in 2 Patients with Addison's Disease and in 1 with Coexisting Addison's Disease and Diabetes Mellitus; abstracted, J. Clin. Investigation **28**: 812 (July) 1949.

4. Sprague, R. G.; Power, M. H.; Mason, H. L.; Albert, A.; Mathieson, D. R.; Hench, P. S.; Kendall, E. C.; Slocumb, C. H., and Polley, H. F.: Observations on the Physiologic Effects of Cortisone and ACTH in Man, Arch. Int. Med. **85**: 199-258 (Feb.) 1950.

corticotropic hormone in six days for acute leukemia. Subsequently, glycosuria disappeared and the fasting blood sugar gradually returned to normal while the hormone was still being administered. Conn, Louis and Wheeler [5] observed impairment of glucose tolerance and fairly pronounced glycosuria in three normal adults who received 120 to 150 mg. of the agent daily for eight to 10 consecutive days. The glycosuria was apparently related in part to lowering of the renal threshold for glucose.

In a case recently studied by Pearson and Eliel,[6] in which the patient, a boy aged 17 years, received exceptionally large doses of cortisone and pituitary adrenocorticotropic hormone as treatment for acute granulocytic leukemia, pronounced glycosuria and ketonuria developed with a blood sugar determination of 505 mg. per 100 cc. and severe acidosis. The patient had not previously been known to have diabetes, nor was there a family history of diabetes. The two hormone agents were withdrawn and 400 units of insulin were employed for treatment of the condition. Death occurred from hemorrhage three days later. The

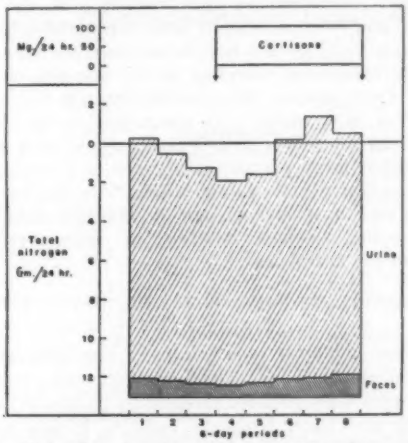


Fig. 2.—Slight effect of cortisone (100 mg. daily) on nitrogen balance in a man aged 34, with rheumatoid arthritis and spondylitis. In this figure, and in figure 3, the daily intake of nitrogen is charted from the 0 Line downward and the average daily excretion (feces below, urine above) from the bottom line upward. A negative balance is therefore indicated by extension of the column above the 0 line, and a positive balance by a clear area below the 0 line.

blood sugar level on the day of death was 300 mg. per 100 cc., and the urine was free of sugar and ketone bodies. At necropsy no definite lesions were found in the pancreas; normal-appearing islet cells were present. In another case studied by McEwen,[7] a girl aged 10 years with acute Still's disease, who was not previously known to be diabetic, excreted up to 90 Gm. of glucose in the urine in 24 hours while receiving cortisone. There was evidence that the glycosuria was in part renal and in part diabetic in character.[8] The changes reverted to normal 22 days after administration of the hormone was stopped.

5. Conn, J. W.; Louis, L. H., and Wheeler, C. E.: Production of Temporary Diabetes Mellitus in Man with Pituitary Adrenocorticotropic Hormone: Relation to Uric Acid Metabolism, J. Lab. & Clin. Med. **33**: 651-661 (June) 1948.

6. Pearson, O. H., and Eliel, L. P.: Personal communication to the authors.

7. McEwen, C.: Discussion on the Effect of ACTH on Juvenile Rheumatoid Arthritis or Still's Disease, in Mote, J. R.: Proceedings of the First Clinical ACTH Conference, Philadelphia, The Blakiston Company, 1950, pp. 393-404.

8. Kass, Ingbar and Finland (Proc. Soc. Exper. Biol. & Med. **73**: 669 [April] 1950) also observed the development of renal glycosuria in a patient with pneumococcic pneumonia and bacteremia during administration of pituitary adrenocorticotropic hormone.

Such exaggerated diabetogenic effects as those just described may indicate that the persons in question had latent diabetes prior to administration of the hormones. Indeed, temporary intensification of preexisting diabetes by cortisone has been observed by Boland and Headley [9] and by Perera and associates.[10] From a practical point

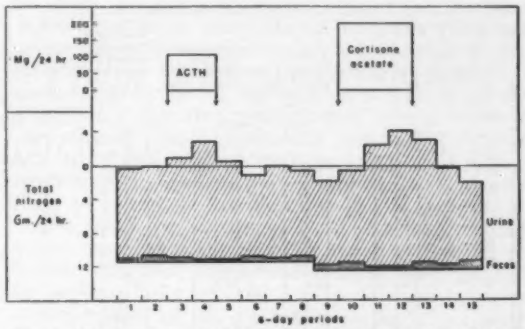


Fig. 3.—More pronounced effects of pituitary adrenocorticotropic hormone (ACTH) (105 mg. daily) and cortisone (200 mg. daily) on nitrogen balance in a woman aged 40, with rheumatoid arthritis.

of view, it is clearly wise to test the urine for sugar at intervals in both diabetic and nondiabetic persons receiving cortisone or pituitary adrenocorticotropic hormone.

Protein.—Our investigations of the influence of the two agents on protein metabolism have consisted of studies of nitrogen balance and the urinary excretion of uric acid, creatine and creatinine.

Cortisone in doses of 100 mg. daily usually induced only slight increases in excretion of total nitrogen (fig. 2). With large doses of cortisone (200 mg. daily) and pituitary adrenocorticotropic hormone (105 mg. daily), however, there was a rather decided loss of nitrogen from the body, indicative of an increase in the catabolism of protein under the influence of these hormones (fig. 3). Likewise, the retention of

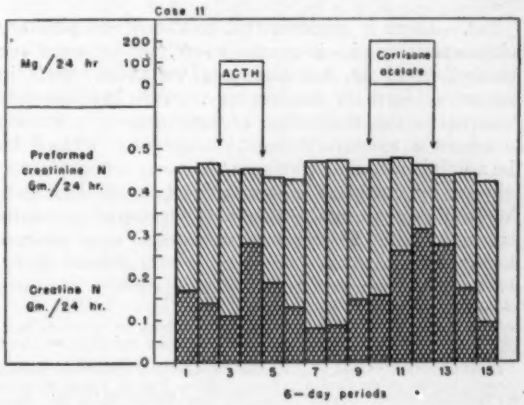


Fig. 4.—Effect of pituitary adrenocorticotropic hormone (ACTH) (105 mg. daily) and cortisone (200 mg. daily) on urinary creatine and creatinine, expressed as nitrogen, in a woman aged 40, with rheumatoid arthritis (reproduced from Sprague and others [4]).

nitrogen which was observed when the effects of the administered hormones had waned is indicative of an antecedent loss of protein.

9. Boland, E. W., and Headley, N. E.: Effects of Cortisone Acetate on Rheumatoid Arthritis, J. A. M. A. **141**: 301-308 (Oct. 1) 1949.

10. Perera, G. A.; Pines, K. L.; Hamilton, H. B., and Vislocky, K.: Clinical and Metabolic Study of 11-Dehydro-17-Hydroxy-Corticosterone Acetate (Kendall Compound E) in Hypertension, Addison's Disease and Diabetes Mellitus, Am. J. Med. **7**: 56-69 (July) 1949.

Pronounced creatinuria was commonly observed when large doses of the hormones were administered (fig. 4). This observation may also indicate increased breakdown of body protein, for creatinuria commonly occurs in association with catabolism of muscular tissue. Likewise, an observed increase in the excretion of uric acid

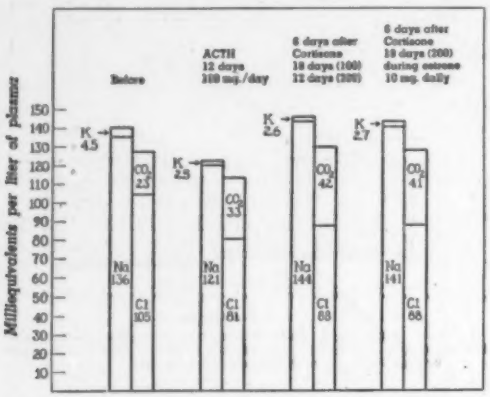


Fig. 5.—Changes in plasma sodium, potassium, chloride and carbon dioxide during and after administration of pituitary adrenocorticotropic hormone (ACTH) and cortisone to a woman aged 45, with rheumatoid arthritis.

under the influence of the hormones, sometimes unassociated with significant change in the level of the serum uric acid, is probably consistent with the same general interpretation.

The effects of the two agents on protein metabolism may be related to the inhibition of hair growth[11] and tumor growth[12] which has been observed in experimental animals, to the development of cutaneous striae in human subjects[4] and to the delayed healing of wounds[13] which has been observed in animal and human subjects during administration of these or related hormones.

Fat.—There is evidence that cortisone and pituitary adrenocorticotropic hormone exert an influence on metabolism of fat, but knowledge of these effects in human subjects is fragmentary. We have already referred to the occurrence of ketonuria in a subject in whom a temporary diabetic state was induced by the administration of cortisone.[6] Severe ketonuria was induced by cortisone in our subjects with coexisting Addison's disease and diabetes.[14] Transient ketonuria was observed by Perera and associates in some patients during administration of 80 mg. of cortisone daily. Thorn and his associates[15] have reported a transient increase in blood ketones during administration of cortisone in five of six patients who had Addison's disease.

Conn and others[16] have reported a decrease in the level of the serum cholesterol esters under the influence of pituitary adrenocorticotropic hormone and have suggested that esterified cholesterol is withdrawn from the blood for the synthesis of steroid hormones by the adrenal cortices when they are stimulated by this agent.

The occurrence of fatty livers in some patients with Cushing's syndrome[17] and in rats treated with the pituitary hormone[18] suggests the possibility that this phenomenon might occur in human subjects as a consequence of prolonged stimulation of the adrenal cortices with the agent. Apparently this has not yet been reported.

Abnormal distribution of fat, resembling that observed in Cushing's syndrome, may occur in patients in whom an excess of adrenal steroids is maintained for prolonged periods by administration of cortisone or pituitary adrenocorticotropic hormone. The trunk and neck appear obese, and the contour of the face becomes rounded. In most instances rounding of the facial contour has been associated with considerable gain in body weight. This has not always been the case, however, for significant rounding of the face was observed in two of our patients during administration of cortisone while the food intake was maintained at a constant level so that there was little or no change in body weight. The altered facial contour is apparently a consequence of deposition of fat in the cheeks. It has been the earliest and most obvious sign of abnormal distribution of fat which we have observed in patients receiving either of the hormones.

EFFECTS ON METABOLISM OF WATER AND ELECTROLYTES

Sodium Chloride and Water.—The characteristic effect of cortisone and allied hormones on electrolyte metabolism was formerly thought to be loss of sodium chloride and water from the body.[19] It now appears that its effects are variable. In some circumstances it may cause a retention of salt and water, sometimes of sufficient degree to produce edema. In other instances, in spite of continued administration of cortisone the retained salt and water may be excreted and edema dis-

TABLE 2.—*Changes in Eosinophil Count in Response to 25 Mg. of Pituitary Adrenocorticotropic Hormone Before, During and After Administration of Cortisone in a Case of Rheumatoid Arthritis and Spondylitis*

	Eosinophils per Cu. Mm.		
	8:00 A. M.	12:00 M.	% Change
Before cortisone	616	123	−80
During cortisone, 100 mg. daily for 20 days	229	257	+12
During cortisone, 100 mg. daily for 32 days	337	341	−4
10 days after last dose of cortisone	151	73	−52
56 days after last dose of cortisone	473	163	−66

11. Whitaker, W. L., and Baker, B. L.: Inhibition of Hair Growth by the Percutaneous Application of Certain Adrenal Cortical Preparations, Science **108**: 207-209 (Aug. 27) 1948.
12. Diller, I. C.; Beck, L. V., and Blauch, B.: Effect of Adrenal Cortical Extract on the Growth of Certain Mouse Tumors, Cancer Research **8**: 581 (Nov.) 1948. Taylor, S. G., III, and Morris, R. S. Jr.: Effect of ACTH in Certain Types of Malignancy, in Mote, J. R.: Proceedings of the First Clinical ACTH Conference, Philadelphia, The Blakiston Company, 1950, pp. 331-336.
13. Ragan, C.: Discussion on Metabolic Effects of Cortisone and ACTH in Cases of Rheumatoid Arthritis, in Mote, J. R.: Proceedings of the First Clinical ACTH Conference, Philadelphia, The Blakiston Company, 1950, pp. 384-385.
14. Sprague, R. G.; Kepler, E. J.; Keating, F. R., Jr., and Power, M. H.: Coexisting Addison's Disease and Diabetes Mellitus: Comparative Effects of Compound E (17-Hydroxy-11-Dehydrocorticosterone) and Allied Substances in 3 Cases, abstracted J. Clin. Investigation **26**: 1198 (Nov.) 1947.
15. Thorn, G. W.; Forsham, P. H.; Bennett, L. L.; Roche, M.; Reiss, R. S.; Slessor, A.; Flink, E. B., and Somerville, W.: Clinical and Metabolic Changes in Addison's Disease Following the Administration of Compound E Acetate (11-Dehydro, 17-Hydroxycorticosterone Acetate), Tr. A. Am. Physicians **62**: 233-244, 1949.
16. Conn, J. W.; Vogel, W. C.; Louis, L. H., and Fajans, S. S.: Serum Cholesterol: A Probable Precursor of Adrenal Cortical Hormones, J. Lab. & Clin. Med. **35**: 504-517 (April) 1950.
17. Gorsuch, M. T.: Cushing's Syndrome: Clinical and Pathologic Investigation of 9 Verified Cases, and Review of the Literature on 91 Additional Cases, Thesis, University of Minnesota Graduate School, 1949.
18. Baker, B. L.; Ingle, D. J.; Li, C. H., and Evans, H. M.: The Effect on Liver Structure of Treatment with Adrenocorticotropin Under Varied Dietary Conditions, Am. J. Anat. **82**: 75-95 (Jan.) 1948.
19. Thorn, G. W.; Engel, L. L., and Lewis, R. A.: The Effect of 17-Hydroxycorticosterone and Related Adrenal Cortical Steroids on Sodium and Chloride Excretion, Science **94**: 348-349 (Oct. 10) 1941.

appear. The factors involved in the variable effects of the hormone on electrolyte metabolism are not well understood. One possible factor is depression of endogenous production of adrenal cortical hormones under the influence of the cortisone.

In our experience the administration of pituitary adrenocorticotropic hormone in doses of 100 mg. daily has almost uniformly caused an early retention of salt and water, followed by increased excretion while the hormone was still being administered or following its withdrawal.

In some clinical circumstances the initial retention of salt and water under the influence of one or the other agent may impose hazard on the patient. This is particularly true in the presence of heart disease or hypertension.

Cortisone in a dose of 200 mg. daily and pituitary adrenocorticotropic hormone in a dose of 100 mg. daily have been observed to cause the development of hypochloremic, hypopotassemic alkalosis, similar in all respects to that observed in some cases of Cushing's syndrome (fig. 5). Thus far all our patients in whom significant alkalosis has developed have been women. In most instances the alkalosis which has resulted from administration of pituitary adrenocorticotropic hormone has differed from that due to cortisone in that there has been some lowering of the level of plasma sodium with the former but not with the latter. After withdrawal of the hormones the concentrations of the plasma electrolytes have reverted to normal, rapidly in the case of pituitary adrenocorticotropic hormone and more slowly in the case of cortisone.

Potassium.—An increased excretion of potassium, with the development of negative potassium balance, has been a characteristic response to large doses of either hormonal agent in all our cases in which balance studies were conducted. The metabolic bookkeeping indicates that the potassium which is lost from the body is derived from the intracellular as well as from the extracellular fluid. The portion of the excreted potassium which originates within the cells is another manifestation of the catabolism of cellular protein which may take place under the influence of these hormones.

EFFECTS ON STRUCTURE AND FUNCTION OF THE ADRENAL CORTICES

Pituitary Adrenocorticotropic Hormone.—The physiological effects of this hormone are contingent on stimulation of the adrenal cortices to increase their output of steroid hormones. Evidence indicates that all known functions of the adrenal cortices are augmented by this agent. Morphologically this stimulation is expressed as hypertrophy and hyperplasia of the cortical tissue. All evidences of stimulation regress rapidly when administration of the hormone is stopped.

Cortisone.—In general, the effects of cortisone on adrenal cortical structure and function are the opposite of those of pituitary adrenocorticotropic hormone. When cortisone or other adrenal hormones which have similar physiological activity are administered to rats, atrophy of the adrenal cortices eventually ensues.[20] A clinical counterpart of this process is seen in patients who have a hyperfunctioning tumor of the cortex of one adrenal gland, particularly when the hormonal activity of the tumor is such as to induce Cushing's syndrome. In such patients the contralateral gland is likely to be atrophic and functionally deficient.[21]

The foregoing observations suggest that cortisone might cause atrophy of the adrenal cortices in the human being and that adrenal cortical function might be depressed during, and for an interval following, administration of the hormone, particularly if large doses had been employed for a prolonged period. We have, in fact, observed four types of evidence suggestive of adrenal depression by cortisone: (1) postcortisone asthenia; (2) depression of urinary 17-ketosteroids during and after administration of cortisone; (3) diminished response to pituitary adrenocorticotropic hormone (test of Thorn, Forsham, Prunty and Hills [22]), and (4) atrophy of adrenal cortices observed at necropsy.

TABLE 3.—*Weight of Adrenal Glands After Administration of Cortisone (Necropsy Cases)*

Sex	Age, Yr.	Diagnosis	Cortisone: Total Amount, Gm.	Cortisone: Days Since Last Dose	Weights of Adrenal Glands, Gm.: Right	Left	Total
F	65	Acute leukemia	3.9	3	4.7	3.9	8.6
F	5	Acute leukemia	4.4	9	1.4	1.3	2.7
F	3	Acute leukemia	3.8	1	1.4	1.5	2.9
F	2½	Acute leukemia	0.135	5	2.4	2.2	4.6
F	18	Acute leukemia	1.35	0	8.8	9.0	17.8
F	17	Lupus erythematosus	4.3	105	4.0	4.9	8.9
M	46	Periarteritis nodosa	2.8 0.885 2.05	12	...	...	12.5
M	48	Periarteritis nodosa	1.875 8.825	22	4.8	3.9	8.7
M	50	Rheumatoid arthritis, hepatitis	1.4 0.7	38	10.0	11.0	21.0

1. *Asthenia Following Withdrawal of Cortisone.*—Beginning a few days to a week after administration of cortisone is stopped, patients may complain of weakness and exhaustion. These symptoms may persist for a few days to several weeks but eventually abate. Although the asthenia cannot be attributed with certainty to adrenal cortical insufficiency, no other basis for it has been apparent in most of our cases. Furthermore, there have been other more tangible evidences of adrenal insufficiency, which are described later.

2. *Urinary Steroids During Administration and After Withdrawal of Cortisone.*—With the exception of cases in which the excretion of 17-ketosteroids was initially low, there was almost uniformly a prompt decrease in urinary 17-ketosteroids soon

20. Ingle, D. J.; Higgins, G. M., and Kendall, E. C.: Atrophy of the Adrenal Cortex in the Rat Produced by Administration of Large Amounts of Cortin, Anat. Rec. **71**: 363 (July) 1938.

21. Kepler, E. J.; Sprague, R. G.; Clagett, O. T.; Power, M. H.; Mason, H. L., and Rogers, H. M.: Adrenal Cortical Tumor Associated with Cushing's Syndrome: Report of a Case with Metabolic Studies and Remarks on the Pathogenesis of Cushing's Syndrome, J. Clin. Endocrinol. **8**: 499-531 (July) 1948.

22. Thorn, G. W.; Forsham, P. H.; Prunty, F. T. G., and Hills, A. G.: A Test for Adrenal Cortical Insufficiency: The Response to Pituitary Adrenocorticotropic Hormone, J. A. M. A. **137**: 1005-1009 (July 17) 1948.

after administration of cortisone in a dose of 100 mg. daily was started.[4] In some cases the levels of 17-ketosteroids remained low for variable periods following prolonged administration of the hormone. These observations would seem to indicate depression by cortisone of at least some functions of the adrenal cortices.

3. *Response of the Adrenal Cortices to Pituitary Adrenocorticotropic Hormone.*—The third evidence of depression of adrenal cortical function by cortisone is a diminished response to a single 25 mg. dose of pituitary adrenocorticotropic hormone as measured by changes in the number of circulating eosinophils (test of Thorn, Forsham, Prunty and Hills[22]). Prior to administration of cortisone, the response to the other hormone was normal in all our patients. During administration of cortisone, the response was abnormal in six of eight tests. After administration of cortisone had been stopped for varying periods of time, the responses were variable, being normal in six tests and abnormal in seven tests.[4] The interval since the last administration of cortisone varied from 10 to 129 days in the six tests in which the response was normal, and from six to 33 days in the seven tests in which the response was abnormal. In all cases in which the test was performed at intervals after administration of cortisone had been stopped, the response eventually became normal. Data in one typical case are shown in table 2.

Thus, if it can be assumed that cortisone does not induce a change in the eosinophils themselves which makes them less responsive to adrenal cortical steroids, the results of these tests suggest that cortisone is capable of temporarily diminishing the responsiveness of the adrenal cortices to exogenous pituitary adrenocorticotropic hormone.

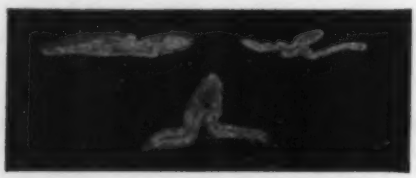


Fig. 6.—Upper: Cut surfaces of atrophic left and right adrenal glands of a girl, aged 5 years, with acute leukemia, nine days after completion of administration of 4.4 Gm. of cortisone. Lower: Cut surface of normal adrenal gland of child of same age, for comparison.

4. *Anatomic Atrophy of the Adrenal Cortices.*—Our associate, Dr. W. A. Bennett, has now had the opportunity to examine the adrenal glands at necropsy in nine cases of acute leukemia, periarteritis nodosa, disseminated lupus erythematosus and rheumatoid arthritis with hepatitis in which cortisone had been administered. The weights of the adrenal glands, together with figures for the total amount of cortisone administered and the number of days between the last dose of cortisone and death, are shown in table 3. Although there is a paucity of consistent data on normal adrenal weights in patients at various ages, and particularly in those dying of the diseases in question, the weights in some of these cases are significantly below recorded figures for supposedly normal adrenal glands.[23] For example, it appears that the atrophy was particularly pronounced in the cases of two children, ages 5 and 3 years, who died of acute leukemia nine days and one day, respectively, after receiving the last dose of cortisone. In these cases the combined adrenal weights were 2.7 and 2.9 Gm. The adrenals in the child aged 5, together with a normal adrenal from a child of the same age for comparison, are shown in figure 6. Histologically, the glands exhibited depletion of lipoid material, particularly in the zona fasciculata, which was significantly narrowed. The glomerulosa was well preserved. Dr. Bennett remarked that the glands had the gross and microscopic appearance of adrenal glands which had become atrophic as a consequence of anterior pituitary insufficiency. Indeed, suppression of the adrenocorticotropic function of the anterior pituitary is probably one of the mechanisms, if not the only one, by which cortisone may induce atrophy.

23. Benner, M. C.: Studies on the Involution of the Fetal Cortex of the Adrenal Glands, Am. J. Path. **16**: 787-798 (Nov.) 1940.

Is the apparent anatomic atrophy and depression of function of the adrenals induced by cortisone of any clinical importance? Experience to date is hardly adequate to provide an answer to this question. We know of no reason to suspect that the alterations of structure and function are not reversible after administration of cortisone is stopped. It is within the realm of possibility that adrenal cortical function in a person who had recently received cortisone might be inadequate under conditions of stress, such as trauma or fever; however, we have not yet encountered such a circumstance.

OTHER HORMONAL EFFECTS

Brief reference to some of the other hormonal effects of cortisone and pituitary adrenocorticotropic hormone will serve to illustrate further that these agents influence the metabolism and function of many, if not all, tissues of the body.

Androgenic Effects.—It came as somewhat of a surprise that cortisone should occasionally induce mild acne and hirsutism in women, effects commonly associated with steroid hormones which have androgenic activity. In our experience more pronounced androgenic effects, such as masculinization of the voice and habitus and enlargement of the clitoris, have not been observed. Those androgenic effects which have been observed have regressed when administration of the hormones has been stopped. Whether cortisone itself has weak androgenic properties or is metabolized in the body to yield androgenic compounds is not known. Pituitary adrenocorticotropic hormone has also been observed to produce androgenic effects, but there is a lack of precise knowledge of what steroid compounds produced by the adrenal cortices under the influence of this hormone are directly responsible for such effects.

Effects on Menstrual Function.—In our original group of patients who received cortisone or pituitary adrenocorticotropic hormones there were 10 women who had normal or almost normal menstrual function prior to the administration of the hormones.[4] Of the 10 women, three became amenorrheic during administration of cortisone. A fourth missed a period which was due a few days before administration of pituitary adrenocorticotropic hormone was started and did not menstruate either during administration of the agent or for a prolonged interval thereafter. Three of the four who became amenorrheic were young girls who had been menstruating three years or less, suggesting that menstrual function is more easily disturbed by these hormones in the young than in the mature woman. Details of the mechanism by which menstrual function may be affected have not been elucidated.

Psychic Effects.—A wide variety of psychic reactions, presumably hormonally induced, have now been observed by us and by others in occasional patients receiving cortisone or pituitary adrenocorticotropic hormone. These have included mild degrees of stimulation, euphoria, manic behavior, depression and frankly psychotic states. Although milder degrees of stimulation and euphoria are explainable as normal reactions to abrupt improvement in physical condition, the more severe reactions obviously cannot be so readily explained. Present evidence suggests that severe reactions are most likely to occur in persons with a background of nervous instability.

SUMMARY

Accumulated evidence indicates that cortisone and pituitary adrenocorticotropic hormone (ACTH) are powerful hormonal agents which are capable of influenc-

ing the metabolism of many, if not all, tissues of the body. Some of these effects have favorable therapeutic implications, others are relatively unimportant, while still others may impose hazard on the patient. It is apparent that an awareness of the widespread physiological potentialities of these agents is a prerequisite for their safe and effective use in the treatment of disease.

EFFECTS OF PITUITARY ADRENOCORTICOTROPIC HORMONE (ACTH) ON THE HYPERSENSITIVE STATE

JOHN EAGER HOWARD, M.D.
A. McGEHEE HARVEY, M.D.
RICHARD A. CAREY, M.D.
and
WALTER L. WINKENWERDER, M.D.
Baltimore

Rich and his co-workers noted that certain anatomic lesions in drug hypersensitivity and in periarteritis experimentally induced by horse serum bear a close resemblance to those of the rheumatic diseases.[1] This observation led to speculation as to the possible role of hypersensitivity in the causation of rheumatic fever, rheumatoid arthritis, lupus erythematosus and periarteritis nodosa. Therefore, when Hench and his group reported the dramatic effects of cortisone and pituitary adrenocorticotropic hormone (ACTH) in patients with these diseases it seemed possible that the clinical improvement might be due to some change in hypersensitivity induced by these agents. Accordingly, experiments were begun to test the effectiveness of pituitary adrenocorticotropic hormone in patients with diseases clearly due to hypersensitive reactions.[2] A brief review of our experience with 23 patients with asthma, 5 with serum disease type of reaction to penicillin, 2 with sympathetic ophthalmia and 2 with ophthalmic and skin sensitivity to atropine forms the basis of this report.[3] Most of the patients were given pituitary adrenocorticotropic hormone; to a few cortisone was given.

ASTHMATIC PATIENTS GIVEN PITUITARY ADRENOCORTICOTROPIC HORMONE

Nineteen patients with asthma have received courses of pituitary adrenocorticotropic hormone. Six of these were given two or more courses. Five patients have received cortisone, and four of these have later been given treatment with pituitary adrenocorticotropic hormone. The asthmatic patients all were suffering with the severe chronic form of disease, intractable to the usual therapeutic measures. All were considered to have asthma of the intrinsic type; in three it was thought to be due to both intrinsic and extrinsic factors.

Results of the first courses of pituitary adrenocorticotropic hormone may be summarized as follows: There was complete remission of all subjective and objective evidence of asthma in 15 of the 19 patients. They usually began to notice some improvement within a few hours of the first dose; complete remission, however, did not occur in one patient until the eleventh day of therapy. Symptomatic therapy was reduced to an absolute minimum after hormone therapy was begun, the patients being allowed but one type of agent such as isopropylarterenol (isuprel®) hydrochloride spray or aminophylline suppository except in exceedingly severe attacks. Reduction in requirement of such adjuvant therapy served as an excellent guide to the clinical course.

The dosage schedule in those patients who achieved a complete remission varied; usually 100 mg. of pituitary adrenocorticotropic hormone (Armour standard)[4] was given daily for the first two days, the amount being gradually reduced to 20 mg., the courses lasting from six to 21 days. The daily dose was always divided into four equal parts, given intramuscularly at six hour intervals. The total amount given to this group of patients ranged from 193 to 1,248 mg.

The duration of complete remission from asthmatic symptoms and signs has varied from three to more than 263 days. There is a rough correlation between the dosage and the duration of remission. The two patients who had the briefest periods of complete comfort received much the smallest and shortest courses of the hormone; however, the patient who received the largest dose manifested beginning asthmatic recurrence two weeks after completion of the course.

Four patients failed to achieve complete remission of their asthma. One was in the sixth and seventh months of pregnancy; although she experienced complete subjective relief on the fifth day of pituitary adrenocorticotropic hormone therapy, the auscultatory rhonchi never entirely disappeared. Two days after therapy was stopped, coincident with an upper respiratory infection, the asthma increased in severity and epinephrine was required. The second patient, who had had asthma more than 40 years, achieved approximately 60 per cent relief but still had to be given spray or injections on humid days. The other two patients who failed to have complete remission from asthma were later discovered to have received only half the scheduled dose of the hormone, owing to an error in assay. To this date none of the patients who have relapsed have had asthma of the same severity as before taking pituitary adrenocorticotropic hormone, as judged by either themselves or their physicians.

ASTHMATIC PATIENTS GIVEN MORE THAN ONE COURSE

Six patients in the first series have been given second or third courses of pituitary adrenocorticotropic hormone. All of these had responded to initial courses with complete remissions. Response to the drug was just as prompt in each instance as with its initial use.

ASTHMATIC PATIENTS TREATED WITH CORTISONE

Cortisone has been given to five patients with asthma. With a single exception, their asthma was similar in type and severity to that of the group who received pituitary adrenocorticotropic hormone. In the first four patients the dose of cortisone was 200 mg. on the

From the Department of Medicine of the Johns Hopkins University and Hospital.

This work was supported in part by a contract between the Johns Hopkins University and the Office of Naval Research and in part by a research grant from the United States Public Health Service.

Read in a Symposium on ACTH and Cortisone before the Section on Experimental Medicine and Therapeutics at the Ninety-Ninth Annual Session of the American Medical Association, San Francisco, June 28, 1950.

1. Rich, A. R., and Gregory, J. E.: Experimental Evidence That Lesions with the Basic Characteristics of Rheumatic Carditis Can Result from Anaphylactic Hypersensitivity, Bull. Johns Hopkins Hosp. **73**: 239, 1943. Rich, A. R.: Hypersensitivity to Iodine as a Cause of Periarteritis Nodosa, ibid. **77**: 43, 1945.

2. Bordley, J. E., and others: Preliminary Observations on the Effect of Adrenocorticotropic Hormone (ACTH) in Allergic Diseases, Bull. Johns Hopkins Hosp. **85**: 396, 1949. Bordley, J. E.; Harvey, A. M.; Howard, J. E., and Newman, E. V.: Preliminary Report on the Use of ACTH in the Hypersensitive State, in Mote, J. R.: Proceedings of the First Clinical ACTH Conference, Philadelphia, The Blakiston Company, 1950, p. 469.

3. Detailed reports of this material are in preparation for publication elsewhere.

4. Supplied as Actarmour by Armour & Company (Dr. John R. Mote).

first day and 100 mg. daily thereafter for seven days. The daily dose was divided into four equal parts and administered intramuscularly at intervals of six hours. A second course with double dosage was given to one patient 45 days after the first course, at a time when the asthma was approximately of equal severity. Only one patient in this group achieved complete subjective and objective remission; his asthma was mild as compared with that of other members of this series. The medicament was given to him primarily to note its effect on a large accumulation of nasal polyps. The other patients experienced only partial relief manifested by reduction in the requirement of antiasthmatic drugs, estimated variously as 25 to 50 per cent improvement. No better clinical improvement than after the initial course was noted during the second course with a double dose of cortisone by the one patient in whom this was tried.

A comparison of the results in this small group of patients with those in the group treated with pituitary adrenocorticotropic hormone would indicate that, at these dosage levels, cortisone compares unfavorably with the pituitary hormone in alleviating the symptoms and signs of chronic bronchial asthma. This conclusion is further substantiated by the results of retreating three of these patients with pituitary adrenocorticotropic hormone 50, 75 and 60 days after the unsuccessful courses of cortisone had been completed. In each of these three instances complete remissions of the asthma were induced. Furthermore, these same patients experienced partial symptomatic relief with this agent considerably earlier than they had with cortisone.

DRUG HYPERSENSITIVITY

Four patients with severe serum disease type of reaction to penicillin were given pituitary adrenocorticotropic hormone, initial doses being 100, 85 and 50 mg. Administration was continued four, five, six and nine days. Total dosage ranged from 145 to 635 mg. Beneficial response occurred in 6 to twelve hours; all subjective and objective signs, including fever, skin and joint manifestations, had disappeared within 72 hours.

A single patient with the same type of reaction to penicillin was given cortisone, 400 mg. the first day and 200 mg. for four succeeding days. No clinical benefit was noted until the third day, at which time urticaria improved slightly, joints were a little less swollen and painful, and fever fell. On the fourth day the temperature fell to normal; there was further minimal improvement in joints and skin. The patient insisted on leaving the hospital after the fifth day, and symptoms subsided gradually, not being entirely absent until five weeks after discharge.

Ophthalmic and skin sensitivity to atropine was reduced in two patients by pituitary adrenocorticotropic hormone. In one patient ocular sensitivity to atropine developed during treatment of sympathetic ophthalmia. During administration of ACTH instillation of atropine was reinstituted without reaction until the hormone dose was lowered to 20 mg. per day, at which time the typical lesions reappeared. At a later time atropine was readministered when the dose of the hormone was 40 mg. per day, and no reaction appeared.

The second patient had manifested dermatologic and ocular sensitivity to atropine and scopolamine during treatment for recurrent uveitis. For four months there had been violent dermatitis of the periorbital and facial skin together with conjunctival reaction. A patch test to atropine produced a severe response similar to the facial lesions. Within 48 hours after pituitary adrenocorticotropic hormone was given, the pericorneal congestion had faded, the erythema and edema of the skin subsided and the intraocular tension became stabilized. On the eighth day of hormone administration, while the patient was receiving 120 mg. per day, the atropine patch test was repeated and only a faint erythema resulted.

Two patients with sympathetic ophthalmia, a disease thought to result from hypersensitivity to uveal pigment,[5] responded with rapid improvement to pituitary adrenocorticotropic hormone. Evidence of inflammation and exudation began to recede within 48 hours, though edema and bogginess of the iris—the so-called organic features—did not seem to be affected.

COROLLARY STUDIES

Certain corollary studies on the patients with hypersensitive reactions while receiving pituitary adrenocorticotropic hormone gave the following results:

Eosinophils.—In the asthmatic patients who received pituitary adrenocorticotropic hormone, the maximum fall in blood eosinophils occurred from the second to the seventh day of drug administration. There was a reasonable correlation between the extent of eosinophil reduction and the degree of clinical improvement. However, toward the end of the course, usually when the dose became lower than 30 mg. per day, the eosinophil count rose although the asthma might still be improving or might remain completely alleviated.

All the patients with hypersensitivity to penicillin had eosinophil counts before medication which were too low for accurate evaluation of the effect of the hormone. Its effect on the circulating eosinophils of the patients with sympathetic ophthalmia and atropine sensitivity was similar to that in asthmatics.

Skin Reactions.—Six of the asthmatic patients were found, before receiving pituitary adrenocorticotropic hormone, to be skin sensitive to inhalants, and one patient to several foods. In five of these patients the immediate skin reactions were significantly reduced while they were receiving the hormone. Immediate skin reactions to bacterial antigens were significantly reduced in 10 of the 15 patients tested during administration of the drug. Delayed 24-hour bacterial reactions were reduced in 11 of the 15.

Of the six patients in whom immediate reactions to pollens and dust were obtained prior to hormone therapy, the serum reagin titer was measured in three instances by passive transfer, using the serum dilution method. The titer was not significantly altered during administration of the hormone, although the immediate skin reactions in two of these three patients were definitely reduced.

Nasopharyngoscopic Observations.—Striking changes were observed by Dr. J. E. Bordley in the nose and nasopharynx of the asthmatic patients during administration of pituitary adrenocorticotropic hormone. The edematous membranes shrank and became normal in color; discharge was reduced, and the lymphoid crypts became more prominent without visible change in the amount of lymphoid tissue present. Nasal polyps shrank, disappearing entirely in some instances. Antral clouding in roentgenograms was reduced and in some cases disappeared altogether.[2]

Antibody Formation.—Dr. George S. Mirick has made studies on the production of antibodies which may be summarized as follows: Antibodies to administered specific Pneumococcus polysaccharide were formed to approximately the same titer and at the same rate in two groups, 16 controls and 15 patients receiving pituitary adrenocorticotropic hormone or cortisone. This was true of both agglutinins and mouse-protective antibodies against Pneumococcus type 2. The latter observation seems of great practical importance and indicates that the two hormones in these doses do not lower the capacity to produce antibodies.

5. Woods, A. C.: Allergy in Its Relation to Sympathetic Ophthalmia, New York State J. Med. **36**: 1, 1936. Friedenwald, J. S.: Notes on Allergy Theory of Sympathetic Ophthalmia, Am. J. Ophth. **17**: 1008, 1934.

Response to the Francis test,[6] manifested by local erythema and wheal formation from the polysaccharide injected intracutaneously at a time when circulating antibodies are elevated, was altered by administration of pituitary adrenocorticotropic hormone. In all controls at two to three weeks, and in six patients tested one to two months after the drug therapy was stopped, the test was positive. Between two or three weeks after vaccination with the polysaccharide, of six patients tested while being treated with the hormone three showed no response at all; the other three manifested only feeble reactions. At the same time all six had good titers of circulating antibodies.

Dr. Bacon F. Chow's studies showed that nonspecific complement rose significantly in all patients studied while being given pituitary adrenocorticotropic hormone. Precipitins to the agent have not developed in any patient.

Metabolic Effects.—In none of the group of patients here reported did there develop striae or glycosuria, and none of the women manifested amenorrhea or hirsutism. One third of the patients became edematous. Significant weight gain occurred in slightly more than one half, varying from 3 to 36 pounds (1.3 to 16.3 Kg.), maximum gain being reached anywhere from the fourth to the seventeenth day of drug administration. There appeared to be no difference between pituitary adrenocorticotropic hormone and cortisone in their propensity to cause sodium and water retention. Significant rises in blood pressure occurred in 10 per cent of the patients. Fasting blood sugar rose more than 20 mg. in one third of the group, maximum rise occurring from the second to the seventh day of pituitary adrenocorticotropic hormone therapy. Acne appeared in four of the group and was severe in one, but it regressed rapidly in all after withdrawal of the drug. Only one patient manifested a fall in serum potassium below 3 milliequivalents per liter; one half of the patients showed rises in serum carbon dioxide of more than 3 milliequivalents per liter, but in none was the rise more than 9 milliequivalents. The hematocrit fell in every instance, the average fall being 7 mm. (Wintrobe); the greatest fall was 10 mm. The degree of fall in hematocrit bore no apparent correlation with the amount of weight gained.

COMMENT

It seems clear that administration of cortisone and adrenal stimulation by pituitary adrenocorticotropic hormone exert beneficial action on the clinical manifestations of bronchial asthma and certain other types of cellular hypersensitivity which are thought to be due to antigen-antibody combination. The site of operation and mechanism of this beneficial action are as yet unknown. The property of "resistance" conferred by either of the hormones appears to be quantitative, lasting for variable periods of time and capable of being "broken through" if the challenge is sufficiently great.

From the evidence thus far obtained, pituitary adrenocorticotropic hormone and cortisone may be profitably used as adjuvants in the treatment of certain allergic conditions, provided neither is used in patients to whom the other physiologic effects of these agents might prove deleterious. Benefit has been obtained in patients with severe bronchial asthma, with serum disease type of reactions to penicillin, atropine sensitivity and sympathetic ophthalmia. A patient with bronchiectasis had severe asthma as a complication, and studies to localize the site and extent of the bronchiectasis could not be performed during treatment with the usual antiasthmatic drugs. After administration of pituitary adrenocorticotropic hormone had resulted in freedom from the asthma, bronchoscopy and pulmonary visualization by iodized oil (lipiodol®) were readily performed.

6. Francis, T., Jr., and Tillett, W. S.: Cutaneous Reactions in Pneumonia: The Development of Antibodies Following the Intradermal Injection of Type-Specific Polysaccharide, J. Exper. Med. **52**: 573, 1930.

SUMMARY

Pituitary adrenocorticotropic hormone (ACTH) and cortisone have been demonstrated to provide clinical improvement in certain hypersensitive states due to antigen-antibody combination. The mechanism of this beneficial action is unknown. This report summarizes the clinical observations on 23 patients with chronic intractable asthma, five with serum disease type of reaction to penicillin, two with sympathetic ophthalmia and two with atropine sensitivity.

USE OF PITUITARY ADRENOCORTICOTROPIC HORMONE (ACTH) AND CORTISONE IN LYMPHOMAS AND LEUKEMIAS

O. H. PEARSON, M.D.
and
L. P. ELIEL, M.D.
New York

The availability of a purified pituitary adrenocorticotropic hormone (ACTH)[1] and of the synthetically prepared adrenal cortical steroid, cortisone[2] (17-hydroxy-11-dehydrocorticosterone) provided means of inducing increased adrenal cortical function in man, in the first instance by stimulating the adrenal cortex to increased activity and in the second by administering a physiologically active, adrenal cortical steroid. Pituitary adrenocorticotropic hormone or cortisone acetate has been administered to 70 patients with various types of neoplastic disease during the past two years at Memorial Hospital. Among this group of patients all the clinical manifestations and metabolic alterations associated with Cushing's syndrome have been observed to develop, which is in agreement with the observations of Sprague and his colleagues.[3]

The clinical and metabolic manifestations of spontaneously occurring Cushing's syndrome have been reviewed by Albright[4] and Kepler and Locke.[5] The production of Cushing's syndrome in man by pituitary adrenocorticotropic hormone or cortisone acetate substantiates the concept of previous investigators that this syndrome is due to an overproduction of adrenal steroids with physiological properties similar to those of 17-hydroxy-11-dehydrocorticosterone. Albright has emphasized that one of the striking features of Cushing's syndrome is decided atrophy of tissues, namely, muscle, skin, bone, lymph nodes and thymus. Although the mechanisms by which the adrenal hormones exert their physiological effects are not known, Albright has

From the Sloan Kettering Institute and Memorial Hospital.

Read in a Symposium on ACTH and Cortisone before the Section on Experimental Medicine and Therapeutics at the Ninety-Ninth Annual Session of the American Medical Association, San Francisco, June 28, 1950.

These studies were supported by grants from the United States Public Health Service, no. C-925(C2); jointly by the Office of Naval Research contract (no. N8-onr-66801) and the Atomic Energy Commission; the Damon Runyon Cancer Research Fund, and the American Cancer Society.

With the advice and assistance of Drs. C. P. Rhoads, Lloyd F. Craver, Rulon W. Rawson, Konrad Dobriner, T. R. Talbot Jr., Joseph H. Burchenal, Henry D. Diamond, George Escher, David Karnofsky, F. C. White, A. T. Petro and J. W. Poppell.

1. Supplied by the Armour Laboratories.
2. Supplied by Merck and Company, Inc.
3. Sprague, R. G.; Power, M. H.; Mason, H. L.; Albert, A.; Mathieson, D. R.; Hench, P. S.; Kendall, E. C.; Slocumb, C. H., and Polley, H. F.: Observations on the Physiologic Effects of Cortisone and ACTH in Man, Arch. Int. Med. **85**: 199 (Feb.) 1950.
4. Albright, F.: Cushing's Syndrome: Its Pathological Physiology, Its Relationship to the Adrenogenital Syndrome, and Its Connection with the Problem of the Reaction of the Body to Injurious Agents ("Alarm Reaction" of Selye), in Harvey Lectures, 1942-1943, Baltimore, Williams & Wilkins Company, 1943, p. 123.
5. Kepler, E. J., and Locke, W.: Chronic Adrenal Hyperfunction, in Williams, R. H.: Textbook of Endocrinology, Philadelphia, W. B. Saunders Company, 1950, pt. 1, chap. 4, p. 180.

postulated that tissue atrophy results from inhibition of tissue synthesis rather than stimulation of tissue breakdown. Metabolic studies on patients receiving pituitary adrenocorticotropic hormone or cortisone acetate have demonstrated that body protoplasm is destroyed.

Animal studies have shown that either hormone inhibits growth in young animals [6] and produces atrophy of lymphoid tissues.[7] Heilman and Kendall [8] have observed that a transplantable lymphoid tumor in mice could be caused to regress by administration of cortisone. Murphy and Sturm [9] have demonstrated that decreased susceptibility to transplantable leukemia can be produced by administering pituitary adrenocorticotropic or adrenal cortical hormones. Law and Speirs [10] were able to produce remissions in spontaneous leukemia of mice with adrenal cortical extracts.

Experimental studies were therefore performed to determine whether increased adrenal cortical function would affect the rate of growth of tumors in man. Preliminary reports of these observations have been published.[11] In this paper, the clinical observations in 70 patients with various types of tumors will be presented.

CLINICAL OBSERVATIONS

Chronic Lymphatic Leukemia.—Eight patients with chronic lymphatic leukemia have received pituitary adrenocorticotropic hormone or cortisone acetate in a dosage of 100 to 200 mg. per day for periods of 18 days to three months. All these patients have shown appreciable shrinkage of enlarged lymph nodes, livers and spleens during hormone administration. In two patients regrowth of tumor masses occurred within two weeks after discontinuation of treatment. In three patients regrowth of lymphoid masses occurred slowly after six weeks to three months. Three patients died shortly after hormone administration was stopped, two with hemorrhagic manifestations and one with intercurrent infection. Four patients have shown responses to two courses of hormone administration. Two patients have had equally effective responses to three courses of treatment over a period of one year of observation. This indicates that refractoriness to administration of these hormones does not develop rapidly.

Some improvement in the hematological picture has been observed in this group of patients. In five patients a rise in reticulocyte count was followed by better maintenance of hemoglobin levels or a spontaneous rise in hemoglobin. In one patient the reticulocyte count rose to 9 per cent and the hemoglobin increased from 7 to 15 Gm. per 100 cc. Seven patients had slight, transient rises in platelet count. In all patients there was a rise in the peripheral white blood cell count during the first two weeks of treatment, in some instances to two or three times the initial level. Thereafter the leukocytes fell to below the pretreatment level in all patients. The differential white blood cell count, which was approximately 98 per cent mature lymphocytes in all patients, did not show improvement. Bone marrow aspirations, which also showed almost complete infiltration with mature lymphocytes, did not show improvement after treatment.

Subjective improvement was noted during the first two weeks of treatment in all patients. This was characterized by a sense of well-being, an improvement in appetite and an improved capacity for mental and physical work. In addition to the three deaths already described, a fourth patient died during a second course of hormone administration as a result of massive hemoptysis from a small pulmonary abscess. Of the four remaining patients, three have been able to resume their usual occupation (laborer, commercial artist and engineer). The fourth patient, although unable to work, is improved and ambulatory. All but one of these patients had previously received roentgen therapy or radioactive phosphorus. Two patients were considered to be refractory to radiation therapy. In several other patients radiation therapy did not seem to be indicated because of hemorrhagic manifestations and low platelet counts.

The therapeutic value of pituitary adrenocorticotropic hormone or cortisone acetate in this disease cannot be adequately evaluated at the present time. Complete remission of the disease does not appear to be obtainable with these hormones. The objective and subjective improvement obtained in this small group of patients suggest that these hormones are useful in the palliation of this disease. Long term observation will be required to determine whether these agents can prolong life in patients with chronic lymphatic leukemia.

Lymphosarcoma.—Six patients with lymphosarcoma have received pituitary adrenocorticotropic hormone or cortisone acetate for periods of nine to 52 days. All these patients showed definite shrinkage of lymphoid tumor masses. Four patients were in a terminal stage of their disease when treatment was started. These patients died during treatment despite transient improvement and objective shrinkage of tumor masses.

One previously untreated patient with disease apparently localized to one side of the neck showed almost complete regression of tumor masses during administration of 100 mg. of pituitary adrenocorticotropic hormone daily for 18 days. No perceptible regrowth of lymph nodes was detected during a three month period after therapy was stopped. Biopsy of two small lymph nodes which remained during this period revealed no significant pathological alteration. During the fourth month after hormone administration, gradual enlargement of lymph nodes was noted and biopsy again revealed changes consistent with lymphosarcoma. Roentgen therapy was given with complete disappearance of the adenopatny.

One patient with severe, generalized adenopathy and splenomegaly showed rapid shrinkage of lymph nodes and spleen during administration of 100 mg. of

6. Wells, B. B., and Kendall, E. C.: The Influence of Corticosterone and Compound E on Somatic Growth, Proc. Staff Meet., Mayo Clin. **15**: 3-4, 1940. Baker, B. L., and Ingle, D. J.: Growth Inhibition in Bone and Bone Marrow Following Treatment with ACTH, Endocrinology **43**: 422, 1948.

7. Dougherty, T. F., and White, A.: Effect of Pituitary Adrenotropic Hormone on Lymphoid Tissue, Proc. Soc. Exper. Biol. & Med. **53**: 132, 1943.

8. Heilman, F. R., and Kendall, E. C.: The Influence of 11-Dehydro-17-Hydroxycorticosterone (Compound E) on the Growth of a Malignant Tumor in the Mouse, Endocrinology **34**: 416, 1944.

9. Murphy, J. B., and Sturm, E.: The Effect of Adrenal Cortical and Pituitary Adrenotropic Hormones on Transplanted Leukemia in Rats, Science **99**: 303, 1944.

10. Law, L. W., and Speirs, R.: Response of Spontaneous Lymphoid Leukemias in Mice to Injection of Adrenal Cortical Extracts, Proc. Soc. Exper. Biol. & Med. **66**: 226, 1947.

11. (*a*) Pearson, O. H.; Eliel, L. P.; Rawson, R. W.; Dobriner, K., and Rhoads, C. P.: ACTH- and Cortisone-Induced Regression of Lymphoid Tumors in Man: A Preliminary Report, Cancer **2**: 943, 1949. (*b*) Pearson, O. H.; Eliel, L. P., and Talbot, T. R., Jr.: The Use of ACTH and Cortisone in Neoplastic Disease, Bull. New York Acad. Med. **26**: 235, 1950. (*c*) Pearson, O. H.; Eliel, L. P., and Rawson, R. W.: Regression of Lymphoid Tumors in Man Induced by ACTH and Cortisone, in Mote, J. R.: Proceedings of the First Clinical ACTH Conference, Philadelphia, The Blakiston Company, 1950. Pearson, O. H.; Eliel, L. P., and White, F. C.: The Response of Neoplastic Lymphoid Tissue to Increased Adrenal Cortical Function, in Symposium on the Adrenal Cortex, Proc. Am. A. Adv. Sc., to be published. Pearson, O. H.; Eliel, L. P., and Talbot, T. R., Jr.: Remission in Acute Leukemia Induced by ACTH, Cancer Research **10**: 235, 1950. Pearson, O. H., and Eliel, L. P.: Metabolic Effects of ACTH in Acute Leukemia, abstracted, J. Clinical Investigation **29**: 838, 1950. Pearson, O. H.; Eliel, L. P.; Talbot, T. R., Jr.; Burchenal, J. H.; Petro, A. T.; Poppell, J. W., and Craver, L. F.: The Use of ACTH and Cortisone in Acute Leukemia, Blood **5**: 786, 1950.

pituitary adrenocorticotropic hormone daily for 18 days. Regression of lymph nodes and spleen persisted for three months after therapy was stopped. During the fourth month slow regrowth of lymph nodes occurred, and a second course of the hormone was equally effective in reducing the size of tumor masses. After a four month interval, during which regression persisted, regrowth of lymph nodes and spleen occurred. In addition, massive right hydrothorax developed, presumably due to enlarged mediastinal lymph nodes. The fluid was aspirated from the chest, and a third course of pituitary adrenocorticotropic hormone was again as effective in shrinking the enlarged lymph nodes and spleen. Regression has persisted during a two month interval since the last course of the hormone, and there has been no reaccumulation of pleural fluid. Evidence of refractoriness to hormone administration has not been manifested in this patient during three courses of treatment over a period of one year. The patient has remained in good health throughout this period.

Evaluation of the therapeutic usefulness of pituitary adrenocorticotropic hormone and cortisone acetate in patients with lymphosarcoma will require further observations.

Acute Leukemia.—The striking shrinkage of lymphoid masses in patients with chronic lymphatic leukemia and lymphosarcoma induced by pituitary adrenocorticotropic hormone or cortisone acetate suggested the trial of these hormones in patients with acute leukemia. It has been found that temporary remissions can be induced with considerable regularity in both children and adults with acute granulocytic or acute lymphocytic leukemia. Monocytic leukemia appears to be unaffected by these hormones. Thirty patients (10 adults and 20 children) with acute leukemia have received one of these agents. Of this group, 13 (nine children and four adults) have shown a good clinical and hematological remission, nine have shown objective clinical or hematological improvement, or both, and eight have shown no response.

Symptomatic improvement usually occurred within the first few days of treatment as evidenced by development of a sense of well-being, improvement in appetite, cessation of bleeding manifestations and a subsidence of fever. Shrinkage in the size of enlarged lymph nodes, spleens and livers occurred within a few days after the start of treatment. Hematological improvement was first manifested by a rapid fall in the number of circulating white blood cells (when initially elevated), an increase in the percentage of mature, circulating leukocytes, a rise in reticulocytes and an increase in platelet count. After two to four weeks of treatment the peripheral blood was frequently normal. Bone marrow improvement was first manifested by the appearance of erythropoietic activity. Within two to three weeks of treatment mature myeloid cells increased in number. In some cases the bone marrow appeared normal during remission, but careful study usually revealed the presence of a few abnormal cells.

Remissions induced by pituitary adrenocorticotropic hormone or cortisone acetate are of short duration, varying from three weeks to two months. Refractoriness to hormone therapy develops rapidly. Although five children have responded to second courses of treatment, in all but one the hormones had to be given for longer periods and in larger dosage before a remission was obtained. Several patients who obtained remissions with a first course of treatment failed to show any response to a second period of hormone administration. Several patients who showed an initial response to treatment, but who failed to obtain a satisfactory hematological remission, relapsed and died while hormone therapy was continued.

Nine patients with acute leukemia, who had become resistant to therapy with folic acid antagonists,[12] have responded to pituitary adrenocorticotropic hormone or cortisone acetate. Similarly, three patients who had become refractory to administration of one of these agents have responded to folic acid antagonists.[12] These observations suggest that the hormones exert their beneficial effects in patients with acute leukemia by a different mechanism than that involved with folic acid antagonists.

Twenty-one patients received pituitary adrenocorticotropic hormone initially and nine were given cortisone acetate. Responses appeared to be equally good with either agent, although usually the response occurred sooner with the former than with the latter. Pituitary adrenocorticotropic hormone was administered in a daily dosage of 50 to 100 mg. to children and 100 to 200 mg. to adults in four divided doses at six hour intervals. Cortisone acetate was given in 100 to 200 mg. amounts daily to children and in 200 to 400 mg. amounts daily to adults, usually in four divided doses. Both hormones were given intramuscularly. It may be concluded from these observations that pituitary adrenocorticotropic hormone and cortisone acetate are useful in the temporary palliation of patients with acute granulocytic or lymphocytic leukemia.

Hodgkin's Disease.—Six patients with Hodgkin's disease have received pituitary adrenocorticotropic hormone or cortisone acetate. During hormone administration four of the six patients showed slight shrinkage of enlarged lymph nodes and spleens. In two patients subsidence of fever and decreased itching of the skin were also noted. One patient obtained temporary relief of mechanical obstruction to respiration. Three patients with far advanced disease died during hormone administration. In two patients with moderately advanced disease prompt recurrence of symptoms and tumor masses followed cessation of hormone administration. One previously untreated patient manifested depression and delusions after six weeks of pituitary adrenocorticotropic administration and committed suicide shortly after the hormone was stopped. These limited observations indicate that either of the two agents may produce slight, temporary improvement in patients with Hodgkin's disease, but lasting beneficial effects have not been obtained.

Plasma Cell Myeloma.—We previously reported [11b] that pituitary adrenocorticotropic hormone failed to produce any significant improvement in one patient with plasma cell myeloma. Postmortem examination subsequent to our report failed to confirm the diagnosis of plasma cell myeloma in this patient: instead, a diagnosis of anaplastic carcinoma was made. Another patient in whom the diagnosis of plasma cell myeloma appeared more nearly certain has shown symptomatic and objective improvement during pituitary adrenocorticotropic hormone and cortisone acetate administration. In this patient administration of the former

12. Studies in these patients were done in collaboration with Dr. Joseph H. Burchenal and will be reported in detail elsewhere.

agent resulted in rapid disappearance of severe pain in the extremities and back, a decided reduction of serum myeloma protein, a rise in reticulocyte count and hemoglobin level and improvement in renal function. The bone marrow, however, has remained infiltrated with plasma cells. When treatment was stopped, there was a recurrence of symptoms within 24 hours. Readministration of the hormone again resulted in striking clinical improvement. Exacerbation occurred a second time on stopping the drug. Improvement was obtained a third time with administration of cortisone acetate, and at the present time the patient feels fairly well on a maintenance dose of 50 mg. cortisone acetate daily.

Neoplastic Diseases in Which the Hormones Have Not Had Demonstrable Beneficial Effects.—Four patients with chronic myelogenous leukemia have received pituitary adrenocorticotropic hormone. Some shrinkage in the size of enlarged lymph nodes and spleens was noted in all four patients. No evidence of improvement in the hematological picture, however, was observed in any of these patients.

Four patients with acute monocytic or acute myelomonocytic leukemia have shown no beneficial effects from receiving either hormone. Seven patients with carcinoma, two of the breast, two of the lung and one each of the prostate, pancreas and adrenal, have not shown demonstrable shrinkage of tumors during hormone administration. Two patients with Ewing's tumor and one each with osteogenic sarcoma, rhabdomyosarcoma, synovial sarcoma, neuroblastoma and malignant melanoma have failed to show any significant change during administration of pituitary adenocorticotropic hormone or cortisone acetate.

COMMENT

Spontaneously occurring Cushing's syndrome has a fatal outcome if untreated. Within our group of 70 patients all the clinical and metabolic manifestations of Cushing's syndrome have been observed to develop as a result of administration of pituitary adrenocorticotropic hormone or cortisone acetate. The use of these hormones is therefore limited by the physiological effects produced, which may in themselves prove fatal. All, or nearly all, of the physiological effects of the agents are reversible when hormone administration is stopped. Certain physiological effects require that administration of the hormone be discontinued; other effects can be controlled without stopping hormone therapy.

Physiological Effects Which Can Be Controlled Without Stopping Hormone Administration.—1. Edema: In patients on an unrestricted diet pituitary adrenocorticotropic hormone and cortisone acetate usually produce decided retention of fluids with edema formation. Occasionally spontaneous diuresis occurs while hormone administration continues. Usually fluid retention continues until the hormone therapy is stopped, when diuresis occurs promptly. Fluid retention is probably caused by a physiological effect on the kidney producing sodium and chloride retention. Pronounced fluid retention can be prevented by restriction of sodium chloride intake (low salt diet).

2. Alkalosis, Hypochloremia and Hypopotassemia: These electrolyte changes occur frequently during administration of pituitary adrenocorticotropic hormone or cortisone acetate apparently as the result of an intracellular potassium deficit. Symptoms and signs of potassium deficit may occur: i. e., apathy, lethargy, muscular weakness or paralysis, abdominal distention and cardiac irregularities. The signs and symptoms of potassium deficit can be alleviated and the serum electrolyte changes corrected by administration of potassium chloride without stopping the hormone.

3. Glycosuria and Hyperglycemia: Diabetes occurs in a small percentage of patients receiving either of the agents. Glycosuria and hyperglycemia are usually moderate in degree and do not require treatment with insulin. The diabetes disappears when the hormone is stopped. In one patient severe diabetic acidosis developed during administration of pituitary adrenocorticotropic hormone. Treatment was stopped, and only moderate amounts of insulin were required to control the diabetic crisis.

4. Atrophy of Tissues: Metabolic balance studies of the effects of pituitary adrenocorticotropic hormone or cortisone acetate in patients with lymphoid tumors have shown that not only lymphoid tumor tissue is destroyed but normal tissues as well. Prolonged administration of either hormone in sufficient quantity may produce severe wasting of muscle and presumably of other normal tissues. Weakness and debility may be associated with this loss of muscle mass aside from the electrolyte changes described above.

A metabolic balance study in one patient with chronic lymphatic leukemia during administration of both cortisone acetate and testosterone has demonstrated that decided shrinkage of lymphoid tumor masses occurred while the patient remained in nitrogen balance. This observation indicates that involution of lymphoid tumor tissue occurred while normal tissue was being built up. Albright [4] has demonstrated beneficial effects of testosterone therapy in patients with Cushing's syndrome. It would thus appear that atrophy of certain normal tissues induced by cortisone acetate administration may be prevented by simultaneous administration of testosterone.

Physiological Effects Requiring Cessation of Hormone Administration.—1. Hypertension: Significant increases in blood pressure during administration of pituitary adrenocorticotropic hormone and cortisone acetate have been observed only in children. Severe hypertension may develop rapidly in children without obvious relationship to duration of therapy, electrolyte changes or the clinical manifestations of Cushing's syndrome. Two children suddenly manifested hypertensive encephalopathy, one during treatment with the former agent and the other during treatment with the latter. There was rapid onset of coma, convulsions, transient hemiparesis, blurring of the optic disks and elevation of blood pressure to levels of 200/140 mm. of mercury. Both patients recovered without residual signs within a few days of stopping the hormones. Significant elevation of blood pressure during hormone administration requires careful observation or immediate cessation of therapy.

2. Mental Disturbances: A sense of well-being even in the presence of debilitating disease is a frequent early effect of treatment with pituitary adrenocorticotropic hormone or cortisone acetate. Sleeplessness is frequently noted during administration of these hormones. After several weeks of hormone administration a state of depression sometimes develops. Two of our patients have committed suicide during such a state of

depression. Delusions have occurred in a few patients after several weeks of hormone administration, e. g., a sense of a peculiar body odor, a sense of shrinking of the extremities to "matchstick" size, a sense of rising into space. Depression, delusions or psychotic manifestations probably demand immediate cessation of therapy.

3. Pyogenic Infections: Lowered resistance to skin infections has been previously noted in patients with Cushing's syndrome. Prolonged administration of pituitary adrenocorticotropic hormone or cortisone acetate may impair the localization and resolution of pyogenic infections. Administration of either of the hormones should not be continued in the presence of infections which fail to respond rapidly to specific therapy.

SUMMARY

Experimental studies of the effects of pituitary adrenocorticotropic hormone (ACTH) and cortisone acetate in 70 patients with various types of neoplastic disease are reported. Administration of these hormones has produced all the clinical and metabolic manifestations of Cushing's syndrome among various members of this group of patients.

Striking temporary shrinkage of enlarged lymph nodes, spleens and livers has been produced as a result of treatment with either agent in patients with chronic lymphatic leukemia, lymphosarcoma, acute lymphatic leukemia and acute granulocytic leukemia. Slight shrinkage of enlarged lymph nodes and spleens in patients with Hodgkin's disease has been observed during hormone administration.

Temporary remissions in patients with acute lymphocytic leukemia and acute granulocytic leukemia have been induced by pituitary adrenocorticotropic hormone and cortisone acetate. Temporary clinical improvement in one patient with plasma cell myeloma has been observed with the use of the two agents.

No significant improvement from hormone administration was seen in patients with acute monocytic or myelomonocytic leukemia, chronic myelogenous leukemia, malignant melanoma, neuroblastoma and several types of carcinoma and sarcoma. These agents are useful in the temporary palliation of patients with acute lymphocytic and acute granulocytic leukemia. Their possible therapeutic usefulness in chronic lymphatic leukemia, lymphosarcoma and multiple myeloma require further evaluation.

The control of the physiologic effects of pituitary adrenocorticotropic hormone and cortisone acetate in man are discussed.

Infinity.—As new stars and galaxies, untold billions of light years distant, are discovered and as still larger and more powerful telescopes are built, there is one mystery that may never be solved by man—the mystery of infinity. . . . It was not so long ago that science taught the indivisibility of the atom. Then we learned that the atom was only Nature's building brick that could be further divided into its components. And then we were told that there are protons and positrons, electrons and neutrons—and no serious-minded scientist would wager that we have reached the end of physical or even theoretical divisibility. For that matter, many begin to doubt that there is such an end. Thus, infinity may work both ways, and no matter how powerful our artificial eyes—the telescope and the microscope—might become, they may never cover more than a limited portion of a band that has no limits and infinity on either side.—*Technical Data Digest*, November 1950, page 4.

EFFECTS OF CORTISONE IN CERTAIN NEUROMUSCULAR DISORDERS

G. M. SHY, M.D.
S. BRENDLER, M.D.
R. RABINOVITCH, M.D.
and
D. McEACHERN, M.D.
Montreal

The effects of cortisone have been studied in 12 patients with muscular or neuromuscular disorders. The therapeutic results in some instances were dramatic, while in others they may throw some light on the mechanism of the conditions involved.

The studies were based on four patients with proximal girdle myopathy which appeared after the menopausal or climacteric period; two with dystrophia myotonica; one with myasthenia gravis; two with disseminated lupus erythematosus with severe muscular involvement; one with juvenile muscular dystrophy with severe contractures, and, finally, two with motor neuron disease manifested by bulbar palsy and amyotrophic lateral sclerosis.

INVESTIGATION

Muscle biopsy was carried out on all patients in order to confirm the clinical diagnosis as closely as possible. Eosinophil counts, basal metabolic rates, glucose tolerance curves and serum sodium, potassium, creatinine and uric acid levels were determined at three to five day intervals. Electromyograms on each patient were obtained before and during administration of the drug and more frequently on the two patients with dystrophia myotonica. All patients were kept on a meat-free diet, and daily 24-hour urine creatine and creatinine determinations were made.[1] Intake and output of fluids were recorded daily. Blood pressures were recorded twice daily. For each patient, an initial electroencephalogram was obtained and one also at the height of medication. Weights were plotted daily. Tests of muscle power were carried out, according to the individual patient's specific weakness, at almost daily intervals. For each patient a cholesterol control period was instituted after cessation of hormone therapy.

GENERAL RESULTS

In all but one case there was a prompt fall in the circulating eosinophils within four to six days after commencement of therapy. The one exception was a case of progressive muscular atrophy in a patient who maintained a persistent unexplained eosinophilia. Glucose curves rose to near diabetic levels in all cases. Our findings, unlike those of Milhorat[2] with pituitary adrenocorticotropic hormone (ACTH), indicated that the creatine: creatinine ratio remained almost constant, a source of disappointment to us. This may have been because levels of cortisone compatible with 150 mg. of pituitary adrenocorticotropic hormone were not used.

In no cases were electroencephalographic abnormalities detected during or after cessation of administration. This is of interest in view of the high percentage of electroencephalographic changes observed by Hoefer and Glaser[3] in their studies with pituitary adreno-

Project no. C-9 of the National Research Council of Canada.
Fellow of the National Research Council of Canada (Dr. Shy).
From the Department of Neurology and Neurosurgery, McGill University, and the Montreal Neurological Institute.
1. Miss Mona Landy and Miss Doris Brophy gave technical assistance.
2. Milhorat, A. T.: The Effect of ACTH in Myotonia Atrophica and in Progressive Muscular Dystrophy, in Proceedings of the First Clinical ACTH Conference, Philadelphia, The Blakiston Company, 1950, pp. 588-595.
3. Hoefer, P. F. A., and Glaser, G. H.: Effects of Pituitary Adrenocorticotropic Hormone (ACTH) Therapy, J. A. M. A. **143**: 620-624 (June 17) 1950.

corticotropic hormone. It should be remembered in this regard that these authors were dealing with different types of cases and that they were stimulating the production of many adrenal steroids in addition to cortisone.

Some fluctuations of serum cholinesterase [4] occurred, with a tendency toward depression. For instance, there was a fall from about 110 to 80 units in the case pictured in chart 1. This did not appear to be very significant, however, when compared with the great depression that can be obtained with anticholinesterases such as diisopropyl fluorophosphate. No appreciable change in basal metabolic rate occurred. Serum potassium and sodium levels showed no notable change. Unfortunately, we were not equipped for urinary potassium determinations, which might have been of greater interest than the relatively stable serum levels. All patients, with the exception of one with disseminated lupus erythematosus, had feelings of well-being and mild euphoria, and with the same exception all showed prompt water retention and weight gain. Only one patient had a significant rise in blood pressure.

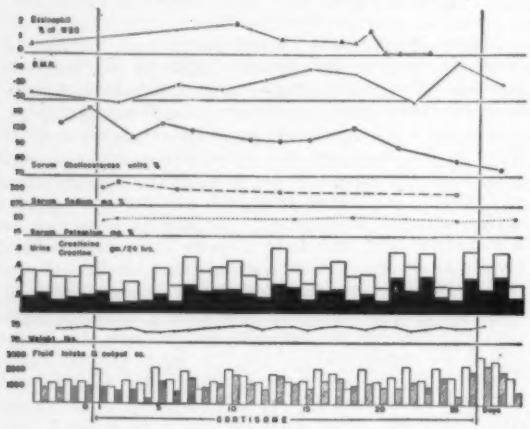


Chart 1 (case 1).—Absence of significant variations in sodium and potassium levels, although the myotonic response entirely disappeared.

It should be pointed out that because of the slow absorption of cortisone acetate, the effects of the hormone take some time, often five or six days, to become manifest. A similar period is required for the effects to wear off when administration is discontinued. Pituitary adrenocorticotropic hormone, on the other hand, works in a period of several hours.

SPECIFIC RESULTS

Dystrophia Myotonica.—Both patients were given 200 mg. of cortisone the first day and 100 mg. on each successive day. This was administered in depots of 50 mg. each. Aside from the general responses noted above, the most striking change was the complete abolition of the myotonic response.

Case 1.—A. C., a housewife aged 39, was admitted with the complaints of progressive wasting and weakness and difficulty of relaxation of all extremities for some six years prior to admission. Her speech had been impaired for the same period. She had been bedridden for about one year. One sister had the same illness, and one brother had voice changes but no other symptoms.

On examination there was marked muscle wasting (weight 76 pounds [34.5 Kg.]), most marked in the sternocleidomastoid, trapezius and shoulder girdle muscles and in the forearms and hands. The patient had a myopathic facies, opacity in the lenses of both eyes, dysarthria and a weak nasal voice. A typical myotonic response was obtained on percussion of the thenar eminence or the tongue. The electromyogram showed characteristic repetitive potentials on insertion of a concentric needle electrode, and these lasted from 70 to 120 seconds in the thenar eminences and in the tongue. The various biochemical and other changes are pictured in chart 1.

Within nine days after commencement of therapy no myotonic response could be noted either clinically or in the electromyogram. The dysphonia had improved until the patient's voice was audible at 30 feet (9 meters), whereas on admission she could be heard no farther than 5 feet (1.5 meters). She claimed that she had increased strength and could carry out certain tasks not previously possible, but no great objective change in muscle power could be made out during the 26 day period of therapy. The rather marked creatinuria was, if anything, intensified during treatment. The myotonia was beginning to return five days after the use of cortisone was discontinued.

Case 2.—G. P., a 32 year old woman, complained of inability to let go of objects in her hand. This had lasted for a period of seven months prior to admission. She had also had progressive difficulty in swallowing and nasal speech for the same period. The siblings of the family had the following afflictions: One man aged 27 had cataracts, nasal speech, testicular atrophy and myotonia; one woman aged 23 had nasal speech and myotonia; one man aged 43 had cataracts and premature baldness, and one woman, age unknown, had myotonia. Two siblings were not examined.

The patient on examination showed slow relaxation of the hand grip and myotonic oscillatory responses on insertion of a concentric needle electrode into the thenar musculature. She had a myotonic contraction on tapping the thenar muscles and the tongue.

All the myotonic phenomena had disappeared in this patient by the eighth day of treatment.

The second patient did not have such profound weakness and wasting as the first, but each felt some increase in muscular power. This was demonstrated clinically by weight and pulley tests. Both patients gained considerably in weight. It is of interest that the biopsy wound in the latter patient was as fresh and unhealed at the end of 12 days' therapy as it was on the day of incision. It healed normally when the administration of cortisone was discontinued.

This abolition of the myotonic response corresponds to the action of the 11-desoxycorticoids (mineral corticoids), as noted by Harvey and Brown [5] in myotonic goats. Since the speech defect did not disappear along with the myotonia, it is probable that it is due to muscle weakness and not to myotonia.

Disseminated Lupus Erythematosus.—Case 3.—O. K., a 20 year old female stenographer, had been in good health until six weeks prior to admission. At that time she began to complain of rapidly progressive weakness and stiffness of the upper and lower limbs, more marked proximally. There was edema of the face, the involved muscles and the overlying subcutaneous tissue. She had noted a red rash over the face, nose, ears and chest. On examination she showed extreme difficulty in talking and swallowing and had to be fed by tube. There was an erythematous, scaly eruption over the upper eyelids, cheek, bridge of the nose, ears, area of the chest, elbows, hands and feet. There was a tachycardia (pulse rate 160 a minute), with some cardiac enlargement. Weakness of the shoulder and hip muscles was so profound that she could not lift her arms or legs from the bed. All involved muscles were swollen and felt "boggy" but were not especially tender on

4. Odom, G.; Russel, C. K., and McEachern, D.: Myogram, Blood Cholinesterase and Effect of Prostigmine in Myasthenia Gravis and Progressive Muscular Atrophy, Brain **66**: 1-17 (March) 1943.

5. Brown, G. L., and Harvey, A. M.: Congenital Myotonia in the Goat, Brain **62**: 341-363 (Dec.) 1939.

pressure. Early contractures were developing, however. There was fever (temperature 101 to 103 F.) and an elevated sedimentation rate. The picture then was one of a constitutional reaction plus an acute dystrophic process in the voluntary muscles. Muscle biopsy disclosed the appearance of a diffuse myositis.

This patient received 200 mg. of cortisone daily for nine days. On the eighth day a profound diuresis began, and on the tenth day the use of cortisone was discontinued and pituitary adrenocorticotropic hormone therapy was initiated in daily doses of 160 mg. This was given in four divided doses. On the sixth day of pituitary adrenocorticotropic hormone therapy, all clinical signs of intracellular excess fluid had disappeared and the weight drop had reached its maximum. The patient then began to retain fluid again, and the moderate weight increase can be seen in chart 2. At no time did the muscles regain their original "boggy" feel. No increase in muscle strength could be detected. At no time was she able to lift her head from the pillow, and she had to be fed by tube until the time of her discharge. The basal metabolic rate of this patient fell, as might be expected from the weight loss. Creatine excretion was lowered to some extent during treatment. The pulse rate fell from 160 to an average of 96 a minute, and the body temperature fell from 101 F. to a normal base line. The skin lesions became less marked. There was thus a marked improvement in the constitutional symptoms but none in the acute dystrophic process in the skeletal muscles, although hormone therapy was continued for a total of 35 days. This patient has since died.

CASE 4.—A. S., a female journalist aged 35, was well until July 1948, two years before admission, when there was rapid onset of pain and swelling in the joints of fingers, wrists and ankles. Sulfonamides were administered, and the patient recovered in August 1949. There was a recurrence, along with fever and a red scaly eruption over the extensor surfaces of the legs, elbows and wrists, with generalized aching throughout the body. This was followed by a scaly red rash over the nose and the malar regions.

From January to April 1950, the patient was treated with desoxycorticosterone acetate (percorten®), 5 mg., followed immediately by intravenous injections of 1 Gm. of ascorbic acid in 10 per cent solution. This treatment was maintained with 4 injections a week, without improvement. In April pregnenetriolone acetate (prenolon®), 200 mg., and salicylates, 40 grains (2.59 Gm.), were given daily, without improvement. She was hospitalized from April 12 to April 22, and at this time had several febrile episodes. No lupus cells were found on sternal puncture or in the buffy coat of the blood. The condition continued and her weight fell from 116 to 96 pounds (52.6 to 43.5 Kg.). At the time of admission to our hospital, on June 4, 1950, it was found that she had been unable to walk since April 22 because of muscular weakness.

Examination showed a systolic gallop rhythm and a questionable pericardial friction rub. The blood pressure was 110 systolic and 70 diastolic. The pulse rate was 100 to 110. The lymph nodes were palpable in the neck, axilla and groin, and they were tender. There was generalized skin and muscle tenderness, and the skin seemed slightly indurated. There was bilateral foot drop with achilles tendon contracture. The extensor hallucis longus, tibialis anticus, extensor digitorum communis groups in the foot and the gluteus muscles at the hips could not move against gravity. There was also severe weakness of the iliopsoas, quadriceps, deltoid, supraspinatus and triceps muscles. All muscles were tender to palpation. The patient was bedridden.

The use of cortisone acetate was started in doses of 200 mg. the first day and 100 mg. daily thereafter. This was administered in depots of 50 mg. each. By the fifth day most of the pain had disappeared, the patient was afebrile, and, unlike the case 3 results, the more severely affected muscles had recovered power against gravity. By the seventh day muscle power against resistance had almost reached a normal level. On the evening of the seventh day the patient walked for the first time in almost four months. The rash now has almost completely disappeared. At the time of writing (ninth day of therapy), she is starting to ascend and descend stairs. Moderate contractures at the various joints have disappeared. In this instance both the constitutional reaction and the profound muscular weakness disappeared with incredible rapidity, and the patient gained 7½ pounds (3.43 Kg.) in the five days preceding the draft of this report.

These two cases should emphasize the facts that muscle changes may be predominant in this little understood condition and that skin changes and other phenomena may be mere highlights pointing the way to diagnosis.

Juvenile Muscular Dystrophy with Collagen Changes.—CASE 5.—J. S., aged 29, gave a history of progressive weakness and wasting of the arms and legs, beginning in early childhood and becoming prominent at 13 years of age. He had been unable to stand or sit unsupported for two or three years. For the past four years he had been unable to flex the neck or spine and was "stiff as a poker." This was apparently due to ligamentous changes or to muscle contractures and not to bony ankylosis. Roentgenograms showed no arthritic changes. No siblings were similarly affected.

Examination showed generalized muscular wasting, without involvement of the intrinsic musculature of the hands and feet. There were flexion contractures of the elbows and knees and fixation of the spine in hyperextension. There was no myotonia. The entire picture was quite different from pseudohypertrophic muscular dystrophy.

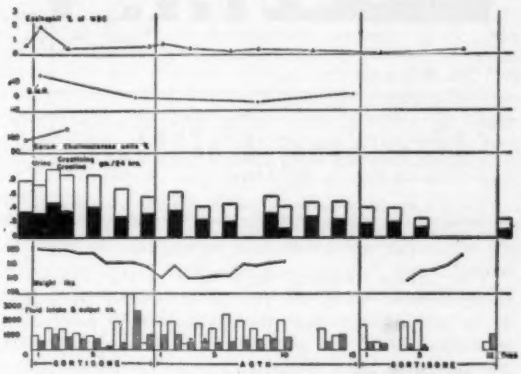


Chart 2 (case 3).—Weight loss coincident with clinical disappearance of the abnormal muscular fluid. Note the rapid fall in circulating eosinophils.

Therapy was started with 200 mg. of cortisone the first day and then 100 mg. each subsequent day until a week before his discharge, when he again received 200 mg. Treatment was continued for 24 days. Creatinuria was intense and appeared to be slightly reduced during treatment, as shown in chart 3. No clinical improvement occurred either in the range of movement or in the muscle strength.

Theoretically this seemed to be our most promising case for trial of cortisone, but perhaps the condition was too advanced.

Progressive Muscular Atrophy—Motor Neuron Disease.—CASE 6.—E. F., a 48 year old nurse, complained of progressive difficulty in swallowing and articulation for one year. Five months before admission she noticed wasting and weakness of the muscles of the hands and, more recently, those of the thigh. Involuntary twitchings had been noticed in these muscles for five months.

On examination it was found that the mouth could not be voluntarily closed and drooled saliva. The eyes could not be closed voluntarily but could close reflexly. The tongue could not be projected, and it showed gross wasting and fasciculation. On attempted phonation, there was no movement of the soft palate or pharynx. The jaw jerk was greatly increased. There was weakness and fasciculation of both forearm and thigh muscles, as well as profound wasting of the intrinsic musculature of the hands. The abdominal reflexes were absent, the deep tendon reflexes increased and the right plantar response equivocal.

At that time the patient presented the terminal stages of motor neuron disease, with both bulbar and pseudobulbar palsy and amyotrophic lateral sclerosis.

During the administration of cortisone no improvement was noted, although a daily dosage of 200 mg. in four divided depots was maintained. Fasciculations were so variable that it cannot be stated that cortisone affected them.

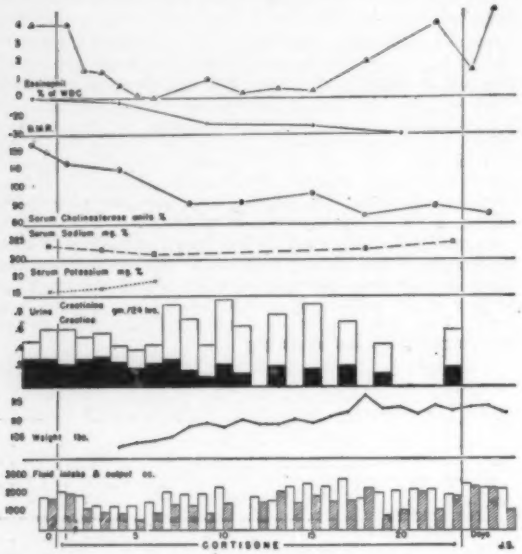


Chart 3 (case 5).—Response to cortisone therapy demonstrated by the eosinophil fall and weight gain of the patient. No improvement in the muscular condition could, however, be demonstrated.

The failure to affect the course of this disorder is in agreement with the results published by others.[6] It is of interest that the patient had unexplained eosinophilia and low grade fever, which persisted during cortisone administration.

Case 7.—L. B., a 38 year old housewife, had a history of progressive weakness and stiffness of the legs and arms, particularly of the hands, for approximately 14 months. She, like patient E. F. (case 6), had had difficulty in speech and swallowing for about ten months.

Examination disclosed wasting and fasciculations of the interosseus, quadriceps and tongue muscles. The deep tendon reflexes were increased, and the plantar responses were extensor. Biopsy demonstrated denervation compatible with motor neuron disease.

The patient received 200 mg. of cortisone the first day and 100 mg. daily thereafter for a total of 21 days. Aside from a mild euphoria, no clinical improvement could be detected.

Myasthenia Gravis.—Case 8.—G. H., a 29 year old truck driver, had noticed progressive weakness and fatigue of the facial and neck muscles, so that his head occasionally fell backward in the morning on rising. He also had difficulty in chewing, swallowing and speaking, and he tired rapidly. He gave a history of some weakness and fatigue of the arms and legs for the past year. The response to neostigmine was good.

Examination showed marked weakness of the facial, masticatory and pharyngeal musculature. There was also marked weakness of the neck muscles and the muscles of the shoulder girdle, most marked in the deltoids. He had a lobulated neoplasm in the anterior mediastinum, visualized on roentgen examination. Prior to the initiation of cortisone therapy, this patient could carry on fairly normal activities with 180 mg. of neostigmine bromide a day.

6. Randt, C. T.; Traeger, C. H., and Merritt, H. H.: A Clinical Study of ACTH on Chronic Neurological Disorders in 7 Patients, in Proceedings of the First Clinical ACTH Conference, Philadelphia, The Blakiston Company, 1950, pp. 595-603.

The patient suffered a severe exacerbation of his myasthenic symptoms while under cortisone therapy. This was so marked that he could not swallow or chew his food or maintain his head erect, even while receiving 270 mg. of neostigmine bromide. At this stage, the sixth day of administration of 100 mg. of cortisone daily, the administration of cortisone was stopped. The patient gradually returned to his preadministration level over a 10 day period. He did not appear to rebound to a state exceeding his precortisone level of power or stamina, as was observed by Torda and Wolff [7] in their studies with pituitary adrenocorticotropic hormone.

All these results may be important in terms of the mechanism of myasthenia gravis, even though they do not offer immediate therapeutic prospects. No decrease in size of the thymic shadow could be demonstrated by roentgen examination at the height of therapy, such as was reported in one case of Soffer and his associates.[8] Adrenal cortex hormones are known to shrink the thymus,[9] but it is only a matter of speculation as to what part this might play in the disease mechanism. The response is demonstrated in chart 4.

Myopathy Appearing After Menopause.—We have coined the term "menopausal myopathy" to describe proximal muscular weakness involving the pelvic and shoulder girdles which appears in the years following the menopause, or the climacteric. Patients with menopausal myopathy have great difficulty in climbing stairs or in rising from a chair, and are subject to unpredictable falls due to sudden giving away of the legs. This condition can be easily missed and may be attributed to the general enfeeblement of age. Strength in the hands and feet remains great, however, and, what

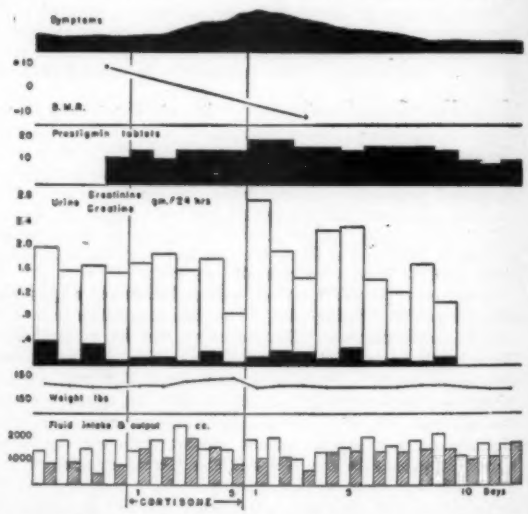


Chart 4 (case 8).—Increase in severity of symptoms in the patient with myasthenia gravis at the fourth to fifth day after cortisone administration. Note the exacerbation occurred in spite of increased neostigmine administration.

is more, the condition appears to be reversible. No wasting of the affected muscles can be demonstrated, as a rule. Following is a typical case.

7. Torda, C., and Wolff, H. G.: Effects of Adrenocorticotropic Hormone of the Pituitary Gland on Neuromuscular Function in Patients with Myasthenia Gravis, in Proceedings of the First Clinical ACTH Conference, Philadelphia, The Blakiston Company, 1950, pp. 575-586.

8. Soffer, L. J., and others: The Effects of Anterior Pituitary Adrenocorticotropic Hormone (ACTH) in Myasthenia Gravis with Tumor of the Thymus, J. Mt. Sinai Hosp. **15**: 73-82 (July-Aug.) 1948.

9. McEachern, D.: The Thymus in Relation to Myasthenia Gravis, Medicine **22**: 1-25 (Feb.) 1943.

on discontinuance of treatment. This observation may be important in terms of the mechanism of myasthenia gravis.

Two women with menopausal muscular myopathy showed decided improvement while being treated with cortisone. One man also improved on the same therapy and dosage, but another man failed to improve. This condition in women previously had been found to respond to wheat germ oil therapy but with a longer time lag.

CAUSES OF FEAR AMONG OBSTETRIC PATIENTS

Chairman's Address

JAMES RAMSDELL BLOSS, M.D.
Huntington, W. Va.

It is a great privilege to have for review almost a half century of activity in any field of human endeavor. One of a previous professional generation may be forgiven if he views with amazement and awe his temerity in having attempted to undertake the responsibilities that he had to assume with an armamentarium so primitive when compared with that at his command today. As one who has been a part of those years of matchless professional progress and scientific accomplishments (even though in such a minor role as has your chairman), I wish to present some thoughts for consideration with the hope that they may have something of constructive value to commend them. Years of experience with a passion for the detailed clinical observation of each patient as an individual entity will of necessity develop a physician's diagnostic acumen, his ideas and opinions and the accuracy of his considered final judgments and therapeutic endeavors.

The wife of a physician had been delivered by one of America's well known obstetricians. For a subsequent delivery he referred her to one of the most prominent protagonists of the psychosomatic school of obstetric practice. Some months after her second delivery she remarked to her former attendant, "I had actual scientific care, but if I should choose my obstetrician I would prefer sympathy and human kindness first and scientific care second." A thought to give one pause, is it not? May it not be possible that those who have been endeavoring to teach undergraduates, interns, residents and postgraduate students are neglecting one of the basic fundamentals of medical training? At times one wonders whether there is not a great need to instill in medical leaders the ability to teach and practice the art as well as the science of medicine.

FEARS WITH PSYCHOLOGIC BASIS

With this thought in mind, humbly making my obeisance to the psychosomaticists of my specialty, it seems timely and germane to discuss some of the causes of fear among obstetric patients. The importance of such a discussion has been particularly impressed on me in recent years by the experiences of my associates and me in the antepartum care of our patients. In the women's magazines the numerous articles dealing with the dangers contingent on the discovery that a prospective mother has Rh-negative blood or the utopian claims for the advantage of continuous caudal anesthesia over saddle block and other technics of analgesia and anesthesia, seem to me to have done harm in that the mental perturbation they have caused among pregnant women is much greater than any good they have accomplished.

The experiences of life over the years reveal that most of the fears which beset everyone from time to time are needless. Many years of obstetric practice convinces me that one of the most important accomplishments of the obstetrician is his ability so to guide his parturient patient through her antepartum period that she shall approach the time of her delivery unafraid, rather "as one who wraps the drapery of his couch about him and lies down to pleasant dreams." The practice of the obstetric art requires much time and infinite patience, and thrice blest is he who has been so fortunate as to have also had previous training and experience in clinical psychiatry. It might be well to require that a certain amount of the time of the obstetric and gynecologic residency be given to this branch of medical study as is done in pathology in relation to the specialty.

Seldom does the obstetrician see cases of such severe antepartum mental disturbance that a psychosis is diagnosed and treatment instituted. Most frequently this state of affairs goes unrecognized and untreated, yet it would seem hardly possible for such experiences not to produce some effect on the average patient.

In no field of my medical experience has it been noted that the home environment and the influence of parental guidance of children is so evident as in the observation of women during the period of professional contact as their obstetric attendant. Prolonged indulgence and protection by unwise parents results in an incapacity to face realities, to realize and evaluate personal responsibility or to make decisions. They are parasites in that they live on the mental and moral strength of others. Naturally, persons in this category are capable of only poor mental adjustment to the unsatisfactory situations and conditions of life and are prone to have a negligible ability for endurance or for making personal sacrifices.

In contrast there are other persons who face all the problems of life unafraid. They solve and overcome the issues, whether great or small. They adapt themselves to meeting sorrow and joy, disappointment, accomplishment, the anxiety and pain of illness, poverty or wealth on an even mental keel. These persons are psychologically evolved or mentally mature.

If one has a clear understanding of these psychologic factors it will aid immeasurably in the approach to and the solution of the maternity patients' problems in the realm of fear. The next important point is that the obstetrician must secure the most complete confidence of his clientele. After this is achieved it is then usually easy for these parturient women to express their mental doubts and fears. With this accomplished the outcome of their struggle to overcome the unhappy mental state is far less in jeopardy. To the patient these fears are very real, and it is a grave error in therapeutic strategy to belittle them or to permit the patient to feel that one is not giving serious and considered thought to their disturbing problems. By all means avoid giving the impression that one regards their fears as ridiculous.

To catalogue all the fears which have been revealed to me by parturient women during the years I have spent in the practice of obstetrics would be an intermina-

Read before the Section on Obstetrics and Gynecology at the Ninety-Ninth Annual Session of the American Medical Association, San Francisco, June 29, 1950.

ble undertaking. Probably among the most frequently encountered may be mentioned that they will lose their willowy figures; that they may lose their sex attraction or function; that their physical appearance during pregnancy will affect the husband's affection and future love for them; that pregnancy may occur at the climacteric period and that there is increased danger of complications when they are past 35 years of age; that if they nurse their offspring the effect on their streamlined appearance will be disastrous, to say nothing of tying them down and interfering with their social activities. In this group should be included the fears of having a deformed or mentally defective infant because of an unsuccessful attempt to produce an abortion, of marking the unborn infant by a fright or shock during pregnancy and of the influence of heredity. This bizarre group of fears is extremely real to patients as individuals and is of important significance in producing mental and emotional conflicts.

BASIC CONFLICTS

It will be of assistance in the care and management of this type of parturient women for one to have some understanding of what these psychic conflicts are and of the mechanism of their development. Despite women's statements to the contrary and their efforts to conceal it from those about them, experienced clinicians, particularly those of the obstetric fraternity, believe that since the dawn of creation the dominant basic feminine instinct is that of reproduction. It is truly primal in all living creatures and in many is more powerful than that for the preservation of life itself. In those women who deny this there is definitely a reason, possibly a subconscious one, which is not in harmony with the idea of motherhood. The woman may be, from environment and training, vain or selfish. She does not wish to make the needful personal adjustments for fear that she may lose the grace and charm which she may be convinced are so outstandingly hers or that she may have to forego the luxury of personal physical comforts which she may be accustomed to enjoy. With such strong and antagonistic feelings one may readily understand how there does develop a psychic conflict, at times of tempestuous character, with the primal maternal instinct. The mentally mature or psychologically evolved woman will, with little or no help, reason out these situations and satisfactorily adjust herself to making all sacrifices of convenience and personal luxuries for the accomplishment and joy of motherhood. With the unevolved person the problem is much more complicated and trying for all concerned. Only experience and a genuine interest in the welfare of his patient can guide the understanding obstetrician.

There is no accurate method for securing a dependable statistical study on the frequency of attempted abortion. Certainly this must be much commoner than is ordinarily realized. It is generally the fear of having a physically or mentally abnormal child which is revealed to the physician in his professional capacity. Careful psychologic study over many years leads me to the conclusion that it is not so much the stated fear of the results of attempted abortion as it is the desire to get the burden of mental guilt off their conscience and to learn the medical attendant's view of the spiritual gravity of their sinful desire in the attempted destruction of the unborn child.

Over the years I have seen no instance in which an unsuccessfully attempted abortion has been followed by the birth of a physically abnormal or deformed child. Many of the resultant children are now adults, and in them I have noted no mental abnormalities which might not much more appropriately be attributed to their inherited familial genes and chromosomes. Certainly there has been no congenital absence of gray matter due to the unsuccessful outcome of an attempt to produce an abortion. A kind heart, an understanding experience and something approaching at least a speaking acquaintanceship with the Almighty will be needed to guide one in answering these unexpressed but momentous questions of spiritual guilt.

The fear of death and the development of complications is another of the more frequent causes of mental unrest in the antepartum period. This fear of death and disease is not an uncommon one for most persons to have, nor equally so is reticence in confessing such a fear. It does not occur to the relatives and close friends of a pregnant woman, as they gossip and recount the unhappy experiences of other women during labor, that she may be having such a difficult mental struggle.

Everyone has had to deal with such situations and at times has been at wit's end as to how to solve the problem. Personally it has proved most satisfactory to discuss these experiences as frankly as may be possible and to point out that countless women have come safely through the ordeal of motherhood. Then call attention to all the safeguards employed by the modern obstetrician to forestall such occurrences and to the special care being exercised in her case to prevent the possibility of such a catastrophe.

Even in this enlightened day the fear of "marking" the unborn child still exists. The witnessing of some accident, being bitten by pets, seeing or being frightened by reptiles and unreasonable cravings for unseasonable foods are still credited as being infallible etiological factors in such occurrences. The psychosomatic approach handles these patients most satisfactorily.

FEARS WITH LEGITIMATE BASIS

Some fears are without the realm of those just discussed, in that there is a basically legitimate reason for them. In this group is the question of possible transmission of syphilitic infection to the offspring. In spite of all the educational efforts being made, I am still having to answer questions on the possibility and probability of such a congenital misfortune. Thanks to the scientific advances in today's therapy of syphilitic infection, one may with confidence assure antepartum patients that this may be erased from the list of their fears.

A word of caution in regard to the interpretation of the routine standard study of the mother's blood for syphilitic infection may not be amiss. In a few rare instances faintly positive reactions may be found during pregnancy in hypoendocrine women. The reaction is usually approximately similar to that noted in an inadequately treated patient in the day of mercury, bismuth and arsenical therapy. Metabolic studies will reveal a minus reading. It will be noted also that the positive serologic reaction disappears a few days after delivery. Further, the blood of the infants will not give this positive reaction. Many years ago a near fatal outcome in administering antisyphilitic therapy to two such patients was a most harrowing experience.

A half century ago, when pregnancy occurred in a person with tuberculosis, diabetes or a cardiac impairment, it was believed that the pregnancy was of primary concern and that the preexisting condition was to be considered as a complication. As time passed this view has changed, and today the obstetrician realizes that the realm of his professional activity is the supervision of the pregnancy as a complication of the preexisting physical impairment of the person. In the management of such patients it is of imperative importance that the closest cooperation of an experienced internist be sought. Few obstetricians will consider themselves professionally competent to guide and direct the treatment of the primarily existing illness. The responsibility for the parturient phase of such a situation seems sufficient for one person to assume.

As I look back over the years nothing is more striking than the changed attitude in regard to pregnancy occurring in the woman ill with pulmonary tuberculosis. Naturally this as a cause of fear is understandable. Formerly it was generally believed that pregnancy allowed to continue practically sounded the death knell for the patient. Thirty or forty years ago physicians were advised that pregnancy complicated by an acute, or even an arrested and quiescent, tubercular infection should promptly be terminated by therapeutic abortion. The observation that among those who refused this drastic therapy a certain number actually seemed to be improved led some obstetricians to advise against this course and to insist on completion of the pregnancy with redoubled efforts in the treatment of the tubercular infection with rest, sunshine, fresh air, food and such tonic therapy as might seem indicated. The results were illuminating and the outcome eminently more satisfactory than those with the previous methods of handling such patients.

Today the scientific management of the tuberculous patient has, to a pronounced degree, removed the fear of pregnancy as a complication. With the development and skilled employment of collapse therapy and the rigid adherence to her hygienic regimen, the patient goes through her pregnancy and delivery with no detectable injury or exacerbation of her tubercular infection. I believe that one of the most outstanding accomplishments in the obstetric management of these patients is the employment of the spinal block method for securing relief from the pain of delivery and the use of the less depressing technics for securing analgesia during labor.

Incidentally, it seems advisable to emphasize most careful examination of the chest of the pregnant woman. Recent surveys indicate that a much larger number of persons have tubercular pulmonary involvement than has been suspected. Studies reported statistically indicate that pregnant women do not present a variation in mortality or morbidity from that in a similar age group of an equal number of nonpregnant women who are tuberculous. Over the past 20 years my experience is in support of this conclusion.

Another outstanding accomplishment of modern medicine is in the technical handling of the diabetic patient when pregnancy occurs as a complication of the preexisting disease. Until the discovery of insulin and until experience was gained in controlling disturbances of metabolism in the diabetic person, the prognosis for these pregnancies was most discouraging.

When one is undertaking the responsibility of caring for a pregnant patient with glycosuria it is of primary importance to determine whether the patient has true diabetes mellitus. In the preinsulin period some clinicians believed that diabetes was responsible, to some extent at least, as a cause of sterility, the frequency of abortions, prematurity, stillbirths and anatomic abnormalities. Certainly the present day therapy for diabetic patients seems to have increased their fertility. My clinical experience with pregnancy as a complication of true diabetes mellitus has not been sufficiently extensive to permit the formulation of a definite opinion concerning the value of the hormonal therapeutic approach to the handling of these patients. Possibly it is not too much to hope that further research in the realm of endocrinology may eventually open this door.

In my years of obstetric prognostication I never have felt more helpless a prophet than when I find myself confronted with pregnancy complicating cardiac disease. At times one observes patients going apparently uninjured through a number of pregnancies and labors although they have valvular lesions which should by the ordinary rules confine them to bed even if they were not pregnant. Others with a seemingly much less serious condition will prove to have no cardiac reserve. Here professional judgment and skill are taxed to the utmost to carry them successfully through their pregnancy. There is no standardized therapy for these patients. Each must be truly individualized and handled as such. Few obstetricians have had a sufficiently extensive cardiologic experience to justify their assumption of such a dual professional role.

It is difficult to understand how a woman with preexisting cardiac disease could go through pregnancy and labor without being injured. The danger of pregnancy is decidedly increased in those who have had previous episodes of cardiac decompensation, regardless of whether they were at that time pregnant or nonpregnant. In the care of these cardiac parturients the most painstaking medical supervision is necessary. With this provided, it has not in my experience been deemed necessary to abort any of them therapeutically.

The problem of labor for the cardiac parturient was most perplexing in the days of inhalation anesthesia. Today with technics of analgesia, and particularly of spinal block and infiltration anesthesia, so scientifically perfected, labor has lost much of the danger formerly present. In my opinion certain of these patients should be delivered electively by abdominal section under spinal or local infiltration anesthesia. This has seemed especially advisable when the patient has severe mitral stenosis, aortic insufficiency or a combination of the two.

THE RH FACTOR

Probably all physicians have been harassed almost beyond endurance concerning Rh-negative blood. The unfavorable publicity noted in most of the articles concerning this condition which have appeared in the magazines of wide lay circulation have been of great harm to the peace of mind not only of parturient women but also of the recently married and of those contemplating matrimony. It is truly remarkable how many questions of a "now suppose" type arise under stimulus of the fear engendered by these magazine articles, when the Rh-negative condition is found to exist.

When the Rh factor was discovered and announced to the members of the medical profession I suspect that most of us felt about as the mathematicians must

have, when Professor Einstein promulgated his theory of relativity. Since then it has become possible for these serologic tests to be made for the investigation of this subject at a cost which is economically practical. As a result of widespread and intensified study by many workers in this field, one may reply to questions of these persons about the Rh factor with the assurance that accumulating investigation and clinical experience make it possible to give a somewhat more intelligent answer and not a more or less oracular guess.

On July 1, 1946 I began a study of the Rh factor. At first the laboratory study of the Rh status of patients was made only when there was a history of previous abortion, prematurity or stillbirths or of previously received transfusions. This plan was followed until Jan. 1, 1948. Since that time the Rh factor has been checked in all women seeking obstetric service who had not been under my supervision subsequent to July 1, 1946. This is now done routinely whether or not the history reveals any of the suggestive leads previously mentioned. This study gave the following information: There was a total of 1,354 (85.86 per cent) Rh-positive and 223 (14.14 per cent) Rh-negative persons. Deliveries for the years 1947, 1948 and 1949 totaled 1,918. The deliveries for the final six months of 1946 were not included, because it was not practicable to study the Rh factor for those mothers first seen previous to July 1, 1946.

Two erythroblastotic infants were lost. One was stillborn; the second lived 36 hours and was atelectatic. The titer of this mother when last determined before the birth of the child was 1:680. Autopsy showed that both these infants were erythroblastotic. A third infant with an erythroblast count of 30 per cent at birth responded to transfusions and now is apparently a normally healthy child aged 2 years.

These studies reveal a number of facts which are not only interesting but of much assistance in discussing these matters with patients. First, a certain number of the husbands may be Rh negative. Three of the 99 Rh-negative parturients of 1949 had Rh-negative mates. Then one must bear in mind that a high percentage of Rh-positive men are heterozygous and will father Rh-negative offspring. The fact that many, possibly the majority, of Rh-negative women may bear two or even more Rh-positive infants before developing a sufficient immunization to produce an abortion or an erythroblastotic infant is to be borne in mind. One must not lose sight of the small mathematical probability of Rh-factor mismatings. It is possibly less than 0.5 per cent. As a final addition to the psychosomatic armamentarium for combating the fears of distraught parturients, the knowledge acquired in this particular field of hematological research enables one to give much encouragement for the survival of erythroblastotic infants by replacement transfusion of carefully selected blood.

It is not out of order to reemphasize the warning of the transfusion danger of giving Rh-positive blood to an Rh-negative person. Much can be done to lower the incidence of sensitization of Rh-negative females, whether infants or adults, by firm insistence that only blood of compatible Rh-negative donors be employed for needed transfusions.

The problem of determining what course to pursue in the delivery of these parturients must of necessity be individualized. When careful study reveals that the mother is not immunized or, if so, that the titer is low and the history does not reveal either a transfusion with Rh-positive blood or a previous erythroblastotic pregnancy, I do not consider it advisable to induce premature labor. My results under such conditions have been most satisfactory by awaiting the normal onset of labor. When conditions are the reverse, it seems advisable to terminate the pregnancy prematurely either by induction and vaginal delivery or by abdominal section, in the interest of the infant and its survival. A word of caution in connection with the decision to terminate the pregnancy prematurely. Do not terminate the pregnancy so far in advance of maturity that the child dies because of immaturity rather than erythroblastosis.

As a result of my personal, though not statistically large, experience I have come to the conclusion that as a cause for fear among obstetric patients the discovery of the negative Rh factor and its implications is not of such serious import as the disturbing publicity leads patients to anticipate.

SUMMARY AND CONCLUSION

Most causes of fear among obstetric patients are needless or not truly existent. However, some of them are not entirely baseless. These must be discussed frankly and encouragingly with patients, in the light of the scientific medical accomplishments of today.

Obstetricians and gynecologists must understand and practice the humanities as well as the science of the medical profession.

418 Eleventh Street East (1).

VERRUCAE, A DERMATOLOGIC PROBLEM

Chairman's Address

CLINTON W. LANE, M.D.
St. Louis

In dermatology there are many unsolved major and minor problems. In the major group are the collagen diseases, the lymphoblastomas and the disturbances of lipoid metabolism, all of which may affect health life. In the minor group are other dermatoses with a less pronounced effect on the general health but which may be most distressing to the patient, disturbing and baffling to the physician. The wart problem is therapeutic rather than diagnostic, not only because treatment is often ineffectual but because it is difficult to evaluate the results of treatment in lesions reacting as peculiarly and inconsistently as warts.

TYPES OF VERRUCAE

Warts are small, almost universally benign papillary overgrowths, which vary in size, color and shape. They are slightly commoner in women, but certain families seem to have a relatively greater resistance to infection with the wart virus than other families. Warts are autoinoculable and transmissible and may disappear without treatment. There are four distinct types: verruca vulgaris, verruca plana juvenilis, verruca plantaris and verruca acuminata.

Read before the Section on Dermatology and Syphilology at the Ninety-Ninth Annual Session of the American Medical Association, San Francisco, June 28, 1950.

Verruca vulgaris, the more commonly observed type, is a raised, circumscribed, solid, round gray or yellowish gray papule varying in size from 2 to 10 mm. The surface at first is flat and smooth but may become scaly, crusted, fissured or cauliflower-like. Warts may be single or multiple; frequently there is a primary "mother wart," which after a variable period of time is joined by other similar satellite lesions. They occur predominantly in children and adolescents and appear most often on the exposed areas, particularly on the hands and fingers, but any portion of the skin surface may be involved. Variants of this type are the threadlike filiform wart of the eyelids and face and the digitate warts which project from the scalp, face and neck.

Verrucae planae juveniles, known as flat warts, are slightly raised, small, flesh-colored, round or angular papular lesions which are distributed over the face, neck, hands and wrists. Almost universally multiple, these lesions occur most often in children and young women. They may be mistaken for vesicles or may closely resemble the papules of lichen planus and, rarely, those of molluscum contagiosum. They produce a "dirty" appearance of the face, when they have coalesced and are located on the chin.

Sites of predilection for verrucae of the plantar type are the padded areas of the soles and heels, less frequently the sides of the feet, the under surfaces of the toes, the palms and palmar surfaces of the fingers. There may be a single wart, but often there are small satellites in the vicinity of the original lesion. Differentiation from a callus and a clavus may be difficult but is facilitated by paring the surface of the verruca. A wart is revealed as a well defined, discrete, gray, round or oval area often containing small dark specks or threadlike lines, which are deposits of blood pigment. The blood has escaped into the basal layer from the dilated vessels of the hypertrophied papillae. If the surface of a callus or corn is pared, a smooth, hard yellow growth containing no blood stains is visualized.

A variant of the plantar wart is the so-called mosaic wart, which has been well described by Montgomery and Montgomery [1]:

> The warty patch is horny and granular with an irregular border and varies in width from 1 to 10 cm. Comparatively painless, the patch is located under the pressure points and may extend onto the toes and behind the heels. It is often mistaken for callus and may be present for years. Paring reveals the intracellular nature of the patch, which consists of many small individual cores so closely grouped that they resemble a mosaic pattern.

Verruca acuminata, known also as condyloma acuminata and venereal wart, occurs chiefly on or about the genitalia and the anus, in the axillas and groins and on the navel. As single or multiple, discrete or confluent, raised, filiform or papillomatous lesions, whose surfaces are often moist and macerated from the secretions of the surrounding organs, they are attached by broad or narrow bases.

ETIOLOGY

Many fantastic theories have been proposed concerning the causation of warts. In the olden days they were often considered as the penalty for indiscretions and sins or as a manifestation of venereal disease. More recently they have been supposedly produced by contact with toads, frogs, lizards and other reptiles and animals. Kühnemann [2] in 1889 claimed that warts were produced by a bacillus, and in 1894 Jadassohn [3] produced warts by subepidermal injections of warty tissue. In 1919 Wile and Kingery [4] reproduced warts by the intracutaneous injection of warty tissue. They postulated that trauma and foreign bodies were portals of entry for an infectious agent, probably a filtrable virus. The incubation period was from four weeks to six months, and in one instance the warts were carried over successfully for two generations. In 1935 Templeton [5] reproduced warts by the intradermal injection of filtrate material and stated that the incubation period may be prolonged from 12 to 20 months. Brain [6] also claimed that it had been established that verrucae were produced by a virus infection. Rulison [7] stated, "The abnormal cellular hypertrophy is due to a local infection with a virus. Whether separate viruses cause the five different forms of verruca or whether the different forms are clinical variations resulting from one virus is unknown." Rudloff [8] believed that venereal vegetations and verruca vulgaris are sister growths due to the same filtrable virus, which manifests itself by papilloma formation on mucous membranes or on thin skin and by wart formation elsewhere.

SYMPTOMS

Verrucae of the vulgaris and flat type seldom produce symptoms severe enough to warrant therapy. Patients present themselves for treatment because they are embarrassed by the appearance and disfigurement of the lesions. This is particularly true if the verrucae are located on the face and hands. The pain and tenderness of plantar warts may be sufficient to seriously hamper the activities of the patient. Verrucae acuminatae may be sensitive, painful and malodorous and may interfere with function.

TREATMENT

The therapy of warts is a difficult problem, and many forms of treatment have been proposed. Wise and Sulzberger stated that "warts are among the most erratic and unpredictable of the dermatoses. Response varies from cases in which a look and a prayer suffice to cases in which lesions persist, recur and even increase despite x-ray, caustics and surgery."

Psychogenic Method.—From the early days of medicine down to the present certain men have believed strongly in the efficacy of the psychogenic method of treatment. In olden times magic was often employed and weird incantations were chanted, often in a graveyard or haunted house. A propitious time for such magic was the waning of the moon. In the modern era the suggestion method was used successfully by

1. Montgomery, A. H., and Montgomery, R. H.: Mosaic Type of Plantar Wart, Arch. Dermat. & Syph. **57**: 397-399 (March) 1948.

2. Kühnemann, G.: Beiträge zur Anatomie und Histologie der Verruca vulgaris, Hamburg and Leipzig, L. Voss, 1889.

3. Jadassohn, J.: Are Verrucae Vulgares Communicable? Verhandl. d. deutsch. dermat. Gesellsch. **5**: 497-512, 1896.

4. Wile, U. J., and Kingery, L. B.: Etiology of Common Warts, J. A. M. A. **73**: 970-973 (Sept. 27) 1919.

5. Templeton, H. J.: Long Incubation Period of Warts, Arch. Dermat. & Syph. **32**: 102-103 (July) 1935.

6. Brain, R. T.: Viruses and Skin Diseases, Brit. M. J. **2**: 191-194 (July 29) 1933.

7. Rulison, R. H.: Warts: Statistical Study of 921 Cases, Arch. Dermat. & Syph. **46**: 66-81 (July) 1942.

8. Rudloff, J.: Venereal Vegetations, Arn. de dermat. et syph. **8**: 23-25 (Jan.) 1948.

Bonjour,[9] who claimed that all warts are curable by hypnosis. He ascribed cures to the lowering of blood pressure. In 1927 Bloch[10] stated that he had cured 44 per cent of the vulgaris type and 88 per cent of the juvenile type by psychogenic therapy. His method consisted of placing the hands of a blindfolded patient on a vibrating motor, although no current was conducted to the person. The warts were painted with a colored fluid, and after the blindfold was removed the patient was told that the warts would disappear when the color faded. Bloch thought that suggestion provides a stimulus to the vegetative centers, which is conducted by the vegetative nerve channels to the warts. These nervous impulses cause biologic changes of a chemicophysical nature and damage the virus. However, Memmesheimer and Eisenlohr[11] studied 140 cases and found that after six months of observation there were more cures in an untreated group than in those treated by suggestion. There is no satisfactory explanation for the spontaneous disappearance of warts or for the cures produced by suggestion, except that the unstable structure of verrucae makes such results possible.

Peroral and Parenteral Therapy.—Peroral medication has many advocates. Drugs reported as producing cures when given orally are mercury compounds, arsenic administered as Fowler's solution (potassium arsenite), arsenic trioxide and acetarsone,[12] dilute hydrochloric acid, thyroid, magnesia, calcium hydroxide solution, arbor vitae, sodium bisulfite, bismuth sodium triglycollamate (bistrimate)[13] and many others. Lurie[14] claimed cures in all of 34 patients who received one to three intramuscular injections of bismuth salicylate. In 1934 Shellow[15] injected potassium bismuth tartrate intramuscularly with good results in only 22.2 per cent of the cases. Sutton[16] endorsed the intravenous injection of neoarsphenamine and sulfarsphenamine, but Allington[17] obtained equally good results from an aqueous yellow solution as from sulfarsphenamine. Other injections reported favorably have been those of autohemotherapy, milk and autolysate material. By the latter method Cormia[18] was successful in 20 per cent of the cases of verruca vulgaris and Biberstein[19] claimed cures in 75 per cent of 139 patients.

Local Therapy.—In 1907 Pusey stated that the only reliable treatment of warts was local destruction. Goldsmith[20] agreed that "Since warts can and often do disappear spontaneously, it is difficult justly to evaluate the efficacy of any treatment that is not directly destructive." Drugs recommended for topical application or superficial puncture are castor oil, potassium hydroxide, acid nitrate of mercury, chromic, nitric and trichloroacetic acids, silver nitrate, phenol, chrysarobin, arsenic paste, Fowler's solution,[21] sulfur, Vleminck's solution and podophyllum.[22] Shellow[15] claimed cures in 91.7 per cent of patients whose warts were injected locally with bismuth potassium tartrate. A 50 per cent solution of urea was beneficial according to Mackay,[23] while Simmons[24] lauded a sclerosing solution. Ethyl chloride, solid carbon dioxide[25] and liquid oxygen[26] have been applied with success, while surgical methods which have been employed effectively are curettage, simple excision, electrolysis, electrodesiccation and actual cautery.

Radiation therapy has many advantages such as ease of application, absence of pain, noninterference with function and avoidance of secondary infection. Therapeutically, roentgen ray and radium are equally efficient, but Osborne and Putnam[27] cited certain advantages of roentgen radiation over radium: 1. Less time is required for treatment; (2) if warts are multiple, large amounts of radium or frequent applications of radium are required, and (3) radium is difficult to apply in some areas and is easy to displace. Most dermatologists prefer and employ roentgen rays, as evidenced by the reports of Hazen and Eichenlaub[28] in 1920, who claimed 93.7 per cent cures, of Michael[29] with 93 per cent cures in 1926 and of Osborne and Putnam,[27] who had 87.7 per cent cures (80 per cent with one treatment and 7.7 per cent with two treatments). The maximum dosage employed by Osborne and Putnam was 8 units, but MacKee[30] advised a maximum dosage of 5 units, with which dosage he had 78 per cent cures in verruca vulgaris and 51 per cent in verruca plantaris. MacKenna[31] gives one dose of 900 to 1,200 r at 100 kilovolts. In a large series of cases of plantar warts Oliver[32] obtained equally excellent results from roentgen and radium irradiation and believed that radiation is the method of choice for this particular type.

PERSONAL EXPERIENCES AND PREFERRED THERAPY

In an experience over a period of 24 years many of the above types of treatment have been employed, some with and many without success. Psychogenic therapy has failed almost universally, probably because the one who employs psychogenic therapy must believe wholeheartedly in its efficacy. In two successful "suggestion cures," which stand out above all others, psychogenic therapy was not intended:

CASE 1.—A young man 21 years of age, a student, who had multiple, large verrucae vulgares of the palms was observed in the late hours of a busy day. He requested that no disabling

9. Bonjour, J.: The Psycho-Vasomotor Theory of Verruca and Condyloma Acuminatum: Experimental Proof, Ann. de dermat. et syph. **1**: 209-219 (Feb.) 1930.
10. Bloch, B.: Therapy of Warts by Suggestion, Klin. Wchnschr. **6**: 2271 (Nov. 26) 1927.
11. Memmesheimer, A. M., and Eisenlohr, E.: Treatment of Warts by Suggestion, Dermat. Ztschr. **62**: 63-68 (Sept.) 1931.
12. Martin, H.: Salvarsan and Sparocid in Treatment of Warts, Dermat. Wchnschr. **111**: 941-946 (Nov. 2) 1904.
13. O'Connor, W. B., and Tweedall, D. C.: Bismuth Therapy of Verrucae: Oral Administration of Sodium Bismuth Triglycollamate (Bistrimate Tablets), J. Missouri M. A. **45**: 25-26 (Jan.) 1948.
14. Lurie, S. A.: Verrucae Vulgares (Palmar and Plantar): Treatment by Intramuscular Injections of Bismuth Salicylate, Arch. Dermat. & Syph. **26**: 95-97 (July) 1932.
15. Shellow, H.: Treatment of Verrucae by Local Injections of Bismuth, Illinois M. J. **66**: 332-336 (Oct.) 1934.
16. Sutton, R. L.: Sulpharsphenamine in the Treatment of Warts, J. A. M. A. **87**: 1127 (Oct. 2) 1926.
17. Allington, H. V.: Sulpharsphenamine in Treatment of Warts, Arch. Dermat. & Syph. **29**: 687-690 (May) 1934.
18. Cormia, F. E.: Autolysate Therapy for Verruca Vulgaris, Arch. Dermat. & Syph. **30**: 44-48 (July) 1934.
19. Biberstein, H.: Autolysate Therapy of Verruca Vulgaris, Dermat. Wchnschr. **99**: 1105 (Aug. 25) 1934.
20. Goldsmith, W. N.: Recent Advances in Dermatology, Philadelphia, P. Blakiston's Son & Co., 1936, p. 387.
21. Paulosky, A. J., and Leider, M.: Treatment of Condylomata Acuminata with Topical Applications of Inorganic Arsenicals, J. Invest. Dermat. **13**: 73-79 (Aug.) 1949.
22. (*a*) Culp, O. S., and Kaplan, I. W.: Condylomata Acuminata: 200 Cases Treated with Podophyllin, Ann. Surg. **120**: 251-256 (Aug.) 1944. (*b*) Sullivan, M.: Treatment of Condylomata Acuminata with Podophyllotoxin, South. M. J. **41**: 336-337 (April) 1948; (*c*) Podophyllotoxin, Arch. Dermat. & Syph. **60**: 1-13 (July) 1949.
23. Mackay, E. M.: Use of Urea (Carbamide) in Treatment of Warts (Verruca Vulgaris), Arch. Dermat. & Syph. **41**: 736-737 (April) 1940.
24. Simmons, N. J.: Anal Warts and Their Treatment with Sclerosing Solutions, M. Rec. **151**: 116-118 (Feb. 21) 1940.
25. Wigley, J. E. M.: General Principles of Treatment of Some Common Skin Diseases, Practitioner **136**: 555-568 (May) 1936.
26. Kile, R. L., and Welsh, A. L.: Liquid Oxygen in Dermatologic Practice, Arch. Dermat. & Syph. **57**: 57-62 (Jan.) 1948.
27. Osborne, E. D., and Putnam, E. D.: The Treatment of Warts, Radiology **16**: 340-345 (March) 1931.
28. Hazen, H. H., and Eichenlaub, F.: Roentgen-Ray Treatment of Verruca Plantaris, J. A. M. A. **74**: 1311-1312 (May 8) 1920.
29. Michael, J. C.: Roentgen Ray Treatment of Verruca Plantaris, Arch. Dermat. & Syph. **13**: 658-660 (May) 1926.
30. MacKee, G. M.: X-Rays and Radium in the Treatment of Diseases of the Skin, ed. 2, Philadelphia, Lea & Febiger, 1927, p. 618.
31. MacKenna, R. M. B.: Modern Trends in Dermatology, New York, Paul B. Hoeber, Inc., 1948, p. 376.
32. Oliver, E. A.: Verruca Plantaris, Arch. Dermat. & Syph. **42**: 302-307 (Aug.) 1940.

treatment be given because he would have to take examinations the following week. Since there were 30 to 40 warts on each hand a soluble bismuth solution was injected into a solitary wart on each palm. He returned in two weeks presenting smooth palms, completely devoid of warts.

CASE 2.—A surgeon with a verruca vulgaris on the distal phalanx of the right index finger refused radiation therapy and postponed the proposed treatment with actual cautery because of fear of pain and inability to operate for several days. An appointment was made for cautery excision, but prior to the date of the appointment he reported that without any therapy the wart had disappeared. This was either a case of spontaneous cure or one in which fear had produced a disappearance of the lesion.

Verruca Vulgaris.—In the treatment of verruca vulgaris local destruction is the method of choice. For small warts including the filiform and digitate types electrodesiccation with or without local anesthesia is the best treatment. For larger verrucae, either single or few in number, a 1 per cent solution of procaine hydrochloride is injected intradermally and the surface of the wart is seared with the actual cautery. The seared covering is then removed with a curet, revealing a red, soft, gelatinous base, which is destroyed down to firm tissue with the same cautery.

Warts in the beard are prone to recur and spread rapidly because they are frequently traumatized in the process of shaving. They are also removed by electrodesiccation or cautery, but after healing has taken place a 1 or 2 per cent mercurial soap is used to cleanse the face and aureomycin ointment is applied after shaving and before retiring. This has decreased recurrences and has produced cures in recalcitrant cases.

Warts around and beneath the nail are difficult to remove permanently. The method which has afforded the most success consists in trimming the overlying nail to provide complete exposure of the wart and in using a superficial application of monochloroacetic acid followed immediately by a 40 per cent salicylic acid plaster. This is kept in place for one week. When the plaster is removed the soft necrotic tissue is trimmed away with scissors and an antiseptic ointment is applied. At the time of application of the plaster, patients are warned that pain may become severe and that, if so, the plaster should be loosened or removed and compresses of boric acid solution be applied. A single treatment will often provide a cure, but two or three applications may be necessary before the wart yields.

In younger children with multiple verrucae vulgares mercurous iodide is prescribed along with a topical application of 20 per cent salicylic acid, 10 per cent resorcinol and 1 per cent mercury bichloride in 95 per cent alcohol. Twice daily this is applied into each wart with the point of a toothpick. The treatment is often augmented by weekly intramuscular injections of a 1 per cent aqueous solution of mercury bichloride. If such a regimen is unsuccessful, an attempt is made to remove the warts by electrodesiccation, but if multiple injections of procaine or many cauterizations are required, it is recommended that the patient be hospitalized and given a general anesthetic. All warts can then be removed painlessly.

Verruca Plana Juveniles.—Verrucae planae juveniles have been more resistant to treatment than any other type of wart. In this group, which occurs predominantly on the face of children, a successful outcome depends not only on the removal of the wart but on a good cosmetic result. Young persons would seem to be ideal subjects for psychogenic therapy, but in my experience it has almost always failed. The methods which have been of the most benefit are mercurous iodide or arsenic trioxide internally combined with small doses of roentgen radiation (44 to 66 r units) once per week for four weeks. On a few occasions, when some of the verrucae have been treated by means of electrolysis or electrodesiccation not only the treated warts but others on the face have spontaneously disappeared. This may be considered as a form of suggestion therapy. However, despite light desiccation the method may produce undesirable pitted scars. Paulosky and Leider [21] have reported success with the use of Fowler's solution locally. Aureomycin internally or locally may prove helpful in curing this type of wart.

Verruca Acuminata.—The therapy of verruca acuminata has been revolutionized by the discovery of the efficacy of podophyllum for this particular type of wart. In 1944 Culp and Kaplan [22a] reported great success by the application of a 25 per cent solution of podophyllum in mineral oil (liquid petrolatum), and they believed the reaction to be specific. Sullivan [22b] in 1948 found that the component of podophyllum responsible for this success was podophyllotoxin. Sullivan [22c] and other investigators discovered that alcohol was a more suitable vehicle for podophyllum than an oily base, as it can be applied into the crevices of the verruca without spreading to the surrounding areas and it dries more rapidly. These are important attributes, because podophyllum produces a pronounced cytotoxic effect on tissues and such reaction should be limited closely to the lesions requiring treatment. The drug may cause edema, redness, ulceration and pain not only of the wart but of the surrounding tissues. For this reason it should be thoroughly washed from the skin surface within seven or eight hours after its application. Facial lesions should be treated cautiously, because when it comes into contact with the eye podophyllum produces severe conjunctivitis, episcleritis and at times corneal ulceration. Paralleling the excellent results of Culp and Kaplan and of Sullivan all the verrucae acuminatae treated by us have disappeared completely, 80 per cent with one and 20 per cent with two applications. A 20 per cent solution of podophyllum in 95 per cent alcohol is preferred.

Plantar Warts.—Plantar warts are best treated with roentgen radiation, but certain requirements cited by Osborne and Putnam are necessary for effective radiation therapy. These are (1) careful paring of the upper horny surface with a scalpel or razor blade, (2) close approximation of lead foil to the periphery of the wart and (3) immobility of areas under treatment. These measures combined with the routine described by Pipkin, Lehmann and Ressmann [33] are used in our practice. The patient lies flat and comfortably on his abdomen, with leg extended and resting on a fixed, padded, raised, wooden support so that the sole is up and horizontal or nearly so. After the surface of the wart has been pared with a razor blade, the margins of the wart are outlined with ink and an opening is cut in a lead

33. Pipkin, J. L.; Lehmann, C. F., and Ressmann, A.: Treatment of Plantar Warts by Single Dose Method of Roentgen Ray, South. M. J. 42: 193-202 (March) 1949.

shield to exactly fit this outline. This shield is held in place with adhesive, and a treatment cone with leaded glass tip is applied firmly to the part. The transparent tip gives the operator the advantage of an unobstructed view of the target. One roentgen treatment and one only of 1,500 r (inherent tube filtration 0.5 mm. Al, 85 kv., 5 ma. at a distance of 8 inches [20 cm.]) is administered and the patient is requested to report for observation in six weeks. If the wart has not disappeared an attempt is made to remove the dried base with a dull curet. Should warty tissue still remain, a 40 per cent salicylic acid plaster is applied for four days and this procedure is repeated several times if necessary. If the above treatment is unsuccessful the wart may then be treated with liquid oxygen or solid carbon dioxide. Should all of these methods fail, then cautery or surgical excision is advocated.

Although removal of the wart is the objective of treatment, nevertheless the severe after-effects of excessive or repeated radiation must not be overlooked. Too many patients have experienced and are suffering from radiation burns of the feet incurred by improper, careless therapy. Although the dosage of 1,500 r does not remove all plantar verrucae, it does give a satisfactory percentage of cures. Also, it is a safe dosage as to date there have been no severe radiation reactions produced. At the time of the treatment each patient is advised, "You are being given a dosage of roentgen rays which in my experience is capable of removing a majority of warts of this type. If it does not do so your wart is probably not radiosensitive, so never at any time in the future allow anyone to give additional radiation, either roentgen ray or radium, to this particular wart." If this or some similar advice is given fewer patients will be experiencing painful, crippling reactions of the feet and fewer operations for the removal of such inflamed tissue will be required.

The mosaic type of plantar wart is resistant to radiation, and for it the method of Montgomery and Montgomery [34] is recommended. After paring the surface of the wart monochloroacetic acid and a 40 per cent salicylic acid plaster are applied. At weekly intervals the macerated surface is trimmed away and the acid reapplied, provided the previous treatment has not produced severe pain. If intolerable pain occurs, wet compresses and a bland ointment are used until the reaction has subsided. When the wart becomes thinner a strong silver nitrate solution (1 grain to 1 minim) is applied. This routine is continued over a period of weeks or months and produces satisfactory results in a majority of the cases.

For multiple warts of the feet of plantar, mosaic and vulgaris types, particularly when accompanied with excessive perspiration and maceration of the interdigital webs, a satisfactory treatment has been to immerse the soles and sides of the feet in a basin containing a 5 per cent solution of formaldehyde. At first this is done daily, but as the feet become drier the immersions are made less often. During the day a bland powder containing 5 per cent magnesium carbonate and 10 per cent boric acid in talc is applied. This has decreased the perspiration and resultant maceration and has provided a good percentage of cures. It is important to warn the patient to be alert for a possible sensitivity to formaldehyde and to stop the treatment immediately if erythema and burning occur.

34. Montgomery, R. M., and Montgomery, A. H.: Common Hyperkeratotic Lesions of the Foot, J. A. M. A. **124**: 756-761 (March 18) 1944.

SUMMARY

1. The four types of verruca are described briefly.
2. Various types of treatment, reported to have been employed with success, are enumerated.
3. The forms of treatment considered to be the most valuable for each type of verruca are described.
4. Certain precautions are given to protect the patient from undesirable results.

3720 Washington Boulevard (8).

PSYCHIATRY IN 1950

C. CHARLES BURLINGAME, M.D.†
Hartford, Conn.

Where does psychiatry stand today? Its position cannot be stated with any exactitude. As a matter of fact, no one can foretell its future further than to say that it will be permanently a part of medicine. Only in regard to the roads leading to the present can one be specific.

COMPARISON WITH OTHER BRANCHES OF MEDICINE

There is no branch of medicine today more in a state of flux, more talked about and more grossly misunderstood than psychiatry. This is true even among medical men, as witness the senior student body in one important medical teaching center seriously debating the question, "Do you, or do you not, believe in psychiatry?" as if it were a cult. Has anyone in modern times ever heard of medical practitioners debating whether or not they believed in surgery or pediatrics? And then one hears much talk about this, that and the other school of psychiatric thought, each accused of claiming to be right and the others wrong. All of this obscures the sound, sturdy development in psychiatry which has been quietly going on for years.

On other branches of medicine there are many groups of workers, each attacking the unknown, complementing the efforts of the others; each striving for a goal, saying to themselves and to each other, "These things we know; these things we do not know," but never saying, "We believe or we do not believe in some doctrine"; each group working with a certain amount of fact to which they add certain "good hunches" and hypotheses; each group having a wary but healthy respect for all other workers in the field; each group striving for new demonstrable scientific facts which can be integrated with the other demonstrated scientific facts in medicine; each group eventually exposing their findings in the full expectation that their work will be submitted to the grueling test administered by other workers, who, as their scientific duty, will attempt to disprove or to endorse the findings. Such is the true scientific basis of all medical progress in American medicine of today.

† Dr. Burlingame died on July 22, 1950. He was president and psychiatrist in chief of the Institute of Living.

Read in the General Scientific Meetings at the Ninety-Ninth Annual Session of the American Medical Association, San Francisco, June 27, 1950.

Because of the emotional storm clouds, the mental thunder and the personality lightning in the field of psychiatry, the members of the medical profession may have the impression that nothing sound and enduring is going on in psychiatry comparable to what is going on in the rest of medicine. Actually, psychiatry is quietly doing a superlative job which merits the confidence and respect of the rest of medicine. The workers in the vineyards of scientific psychiatry have multiplied tremendously in the 40 years and more since I entered the then-rather-desolate field. May I here interpolate that psychiatry is America's prize and oldest example of socialized medicine, which has been the state responsibility for over 100 years. This has been publicized as America's prime medical scandal and example of medical and social lag, in spite of the struggle of conscientious psychiatric leaders.

PSYCHIATRIC PROPAGANDA

Most workers in psychiatry are keenly aware of the unsoundness of the wave of psychiatric propaganda which has swept the country, with its unfortunate reactions. They have been quite aware of the accusations that some psychiatrists have been indiscreet and immodest in their claims. Again, broadcasting such statements as "see a psychiatrist early," "one in 11 persons needs to see a psychiatrist," "one in 20 will spend some time in a mental hospital" (then representing the state hospitals as snake pits) and "one in two hospital beds is psychiatric" has increased the anxiety of a large band of delicately balanced persons. When these remarks are followed with statements that "there are only five or six thousand psychiatrists in the country" and "the average person cannot possibly see one" anxiety is piled on anxiety, with no chance of its being liquidated. In the cancer drive, if the slogan "thump that lump" is popularized, the inability of the patient to see a physician will not make the benign lesion malignant. But one says "thump that lump of anxiety" and because of the shortage of psychiatrists the patient cannot get one to do so. Anxiety has its own malignant tendency to grow upon itself, even though to begin with it may have had no serious import. In short, propaganda, producing an anxiety that cannot be liquidated, creates the very psychiatric condition which it purports to eliminate. These things, however, although they may have been done under a psychiatric banner, should not be charged to psychiatry, the medical specialty.

Psychiatry has become much confused in the public mind with things nonmedical. One finds the papers carrying the story of the psychoanalysis of a motion picture star's pet pup, who was found to be suffering from an acute anxiety neurosis. Again, more recently, the two flyers who had been interned for 18 months in Communist China were interviewed on the radio. The master of ceremonies brought out time and again that, even without freudian training, the boys psychoanalyzed each other and thereby were prepared to analyze their captors and effect their escape. This goes on and on, until the serious-minded medical practitioner, surfeited with this sort of thing, prayerfully mutters, "O death, where is thy sting?" I sometimes think it might be well to substitute the term psychological medicine for the term psychiatry, in order to disidentify this branch of medical practice from the flotsam and jetsam on the psychiatric sea.

DIAGNOSTIC PROBLEMS

In 1950 psychiatry is forced to use diagnostic terms which are merely descriptive of a condition and, with a few exceptions, it has no disease entities corresponding to the diagnosis of pneumonia or appendicitis. Even with this handicap one can treat and prognosticate with improving exactitude. I feel encouraged that, as an etiological and somatic pathologic basis is established, disease entities will be lifted out of the manic-depressive basket, the dementia precox basket and the psychoneurotic basket.

It is known that psychoses and other psychiatric conditions can now be experimentally produced in animals and human volunteers, and the process reversed at will. This at long last parallels what is considered to be a scientific necessity in the study of somatic disease and is reminiscent of Koch's postulate for scientific deduction. These psychotic states can be induced by a variety of methods and agents, such as pituitary adrenocorticotropic (ACTH) and other hormones acting on the adrenocortex, drugs such as diisopropyl fluorophosphate and lysergic acid, and even planned, persistent emotional traumas. Most significant is the fact that these artificial psychoses can be broken up and the syndromes dissipated by some of the present day psychiatric therapies, such as electroshock. Furthermore, these synthetic psychoses can be influenced by psychotherapy, retraining methods and environmental controls. Although no thoughtful man of science will take this single group of facts and consider the battle won, he cannot fail to see the opportunity thus provided to march a whole army of hard-headed scientific workers onto the field.

Today the actual mechanism of mental disease still is not understood, but many investigations of promise are being conducted. Among these is the study of endocrine glands in the production and control of so-called mental disease, i. e., the observed significant alterations in adrenocortical function with the pituitary adrenocorticotropic hormone, sex steroids and other hormones. These are only examples of studies in progress which are closing in on the unknown mechanistic factors of mental disease.

ETIOLOGIC ASPECTS

There is little irrefutable knowledge of the causation of mental disease, but momentarily it is known that there are conditions which are called mental disease. It is known further that these may be produced by bacterial invasions, by dietary dystrophies, by exogenous and endogenous toxins, by physical trauma and fatigue, and also by psychological trauma and emotional strain. On the other hand, the knowledge that physical disease can be produced by emotional causes, which has recently been popularized as psychosomatic medicine, is as old as recorded medical history. Even the term psychosomatic medicine was used over a century ago; then the fashions changed, but now psychosomatic medicine is once more in style. Because of a duality of language, with separate words for mental and bodily processes, physicians came to think of the mind and body as separate, with diseases of the mind and of the body also separate.

There is a psychological side, sometimes minimal, sometimes great, to all so-called somatic ills, whether typhoid with its delirium, gastric ulcer, pneumonia, a malignant lesion or a fracture. And psychiatrists know,

or should know, that there is no such thing as a mental disease without some somatic recording. After all, the body is the vehicle of the mind, and it is a scientific impossibility to conceive of the mind and mental disease floating around in a state detached from that vehicle. It would not be flattering to the psychiatrists' powers of deductive reasoning to assume that there is no somatic accompaniment to so-called mental disease just because, with the still imperfect diagnostic methods that are available, it is impossible to identify it. The laboratory observations of today are confirming the thesis that disease is neither mental nor physical but that all disease has different symptomatologic weightings between the psychological and the somatic.

To consider only two types of laboratory investigation, with cytochemistry and the ultraviolet spectromicroscope, psychiatrists are now able to see changes in protein metabolism of the nerve cell as a result of acoustic trauma and fatigue. Can it be that the time is approaching when it will be possible to see positive evidence of mental illness in the nerve cell under the ultraviolet microscope?

The effect of environment on the body, and thus by implication on mental disease, is also being demonstrated. In one experiment Norway rats bred for generations in the effete environment of Baltimore laboratories were found to have only a fraction of the adrenocortex of their wild, "alley-ashcan" distant cousins. When exposed to a new environment, the wild rats with their large adrenals distrusted each other, were overly aggressive, had disturbed behavior patterns and were unable to survive a change in diet. Briefly stated, in rat society they may have been guilty of "psychotic" behavior. In turn, the cultured rats, with their small adrenals, were overly submissive and timid, manifesting their own less vigorous signs of inadaptability. Are the scientific laboratories about to take out of the field of theory and speculation this whole question of the effect of environment on disease and health? Man is an adaptable animal, but just how adaptable?

Impressive indeed is the voluminous literature which each year records the observations and experimentation of laboratory workers. It records studies of changes in behavior, in emotional patterns and in social relationships through the use of surgical operations, chemicals, environment and training. So extensive is it that it would be prohibitive to do more than mention it.

PSYCHOTHERAPY

First among the therapies in 1950 let me mention psychotherapy. In the minds of much of the public and some of the profession, psychotherapy and psychoanalysis have come to mean one and the same thing. This would be analogous to saying that surgery and appendectomy are synonymous. One of the fractions of psychiatry is psychotherapy, and one of the types of psychotherapy is psychoanalysis; within the field of psychoanalysis there are several schools of thought. I believe that psychotherapy, no matter what its form, is essentially personal tutoring, by which I mean understanding guidance in personality development. Today psychotherapy is not an exact science by any means; nevertheless, some form of psychotherapy, even with its imperfections and lack of exactitude, is indispensable.

In the past there has been more heat than enlightenment generated by the vigorous differences of opinion regarding psychotherapy. However, there is beginning to be more enlightenment and less heat with the critical, nonemotional evaluation of results. There has been decided development along the line of simple, practical psychotherapy aiming at positive results in less time and at lower costs. This development, with due consideration for time and money involved and for practicality, has become a prime necessity. The claim that psychotherapy is solely a lucrative way of entertaining suburban ladies is not justified.

But psychotherapy, important as it is, is not the only psychiatric therapy. I am reminded of a little discussed statement of Sigmund Freud in 1920, when, speaking of the endocrine system, he stated, "The structure of psychoanalysis that we have erected is really only a superstructure which at some future time must be placed upon its organic foundation."

Psychotherapy enters into a partnership with rehabilitation. To draw a parallel, the modern surgeon would no longer consider it good surgical care to operate on an elbow and have it heal stiff, useless and in the way. His objective is toward the restoration of function. So it is in psychiatry. The procedure has become extremely practical. Decades ago it was learned that "loafer's delight," either in or out of a hospital, was the greatest foe to mental health and successful psychiatric therapy. Psychiatrists are thinking in terms of restoration, that is, the development of social function, not just keeping the patient busy weaving raffia baskets or rugs, except he be a Navajo Indian for whom that might be a vocation.

Psychiatrists have taken a leaf from the book of modern industry, and now they estimate a person's various capacities, develop and direct his abilities, and, in brief, equip him to go out and do what he must do as a productive member of society. Similar thinking and similar purposeful technics are being used to obviate the necessity for hospitalization. It is no longer considered good psychiatric practice, or good medical practice for that matter, to say "you need a vacation," which once used to be the universal recipe when the medical advisor did not know what else to say. Sardonically enough, however, "loafer's delight" or "do nothing for a while," with its etiological potentialities for mental and physical illness, is gradually receiving great impetus through pension schemes with enforced retirement. These erroneously assume that a man's goal is ultimate idleness. Too often, sudden decompression from carrying heavy responsibility is producing an emotional caisson disease which is gradually appearing in all doctors' offices in all specialties, even though not generally recognized. At least part of the cure is to have the patient reassume real responsibility.

PSYCHOSURGERY

Surgery of the mind is much in the limelight today. The debate about its usefulness should be just about over, with the award last year of the Nobel Prize to Egas Moniz, the originator of psychosurgery. The so-called "ashcan selectivity," which recommended psychosurgery in the long-standing cases in which there was nothing to lose, has moved decidedly in the direction of something more scientific. It is now known that many patients with chronic conditions do not benefit from surgical intervention and that some of those who have more recently become ill may well profit from operation. The temporary blocking out of certain cortical areas of the brain through local anesthesia is

one of the many studies, all leading toward a more refined and positive selectivity. Those sophisticated in the procedures have developed a sense of balance extremely necessary in consideration of the sometimes spectacularly good results. Simultaneous with improved selectivity there have been developed several different operative technics from which to choose. All, however, have the objective of producing a new malleability that will permit the restoration of a patient into useful society. With some of the newer technics, it is not uncommon to operate on a patient in the morning and to have him up in the afternoon and in retraining classes the next day. To the question "Will psychosurgery change the personality of this sick person?" the answer is, "I hope so." To the question "Will the patient be made into a vegetable?" the answer is, "to my knowledge no sophisticate in the field has ever seen the operation produce such a metamorphosis." With some of the technics there is not even measurable intellectual impairment. Reeducation after psychosurgery is coming to be regarded as essential in order to break up bad habit patterns, the by-product of mental disease, and to establish socially acceptable habit patterns. To ignore the potentialities of psychosurgery is to be negligent. On the other hand, uncontrolled enthusiasm is frowned upon today.

Shock therapies are now firmly entrenched both in institutional and in office practice. The indications for insulin, pentylenetetrazole (metrazol®), electric shock therapy or their combinations are more specific. No longer does a psychiatrist feel helpless when a depressed or suicidal patient comes to him. He often uses one of the forms of shock therapy to protect the patient from self destruction in the emergency. Simultaneously he moves in with his indispensable psychotherapy or chemotherapy or other psychiatric procedures. The erroneous impression has originated that psychiatrists generally are using the shock therapies to the exclusion of all other forms of treatment. In reality, these are being used in conjunction with all other available forms of therapy. It still is not known how shock therapy works—possibly it is a physiological mechanism, operating through the autonomic or endocrine system. In the shock therapies, also, strides are being made in the matter of selectivity. With the aid of epinephrine and methacholine (mecholyl®) chloride, the time may be approaching when success or failure with shock therapies can be most accurately foretold.

It has long been the dream of psychiatrists to find some drug which would cure mental illness. Such a drug has not been found. The idea of finding any one drug does not appeal to reason. However, the chemotherapists of today are discovering that a number of drugs such as ether administered intravenously, mephenesin, lithium salts, malononitrile and histamine have a definite effect on various phases of mental disorders.

The over-all picture might be summed up by saying that psychiatriy in 1950 embraces psychological, surgical, educational, chemical and physical therapies, all based on a sound knowledge of man's body as well as his mind.

PREVENTIVE PSYCHIATRY

Preventive psychiatry today is more of an aspiration based on multiple theories than a body of fact that can be demonstrated. Be that as it may, I am certain that most preventive psychiatry is, or will come to be, practiced by men in the other branches of medicine. It is those in other branches of medicine who have the opportunity to prevent psychiatric conditions so far as they are preventable. These men know the disease, but must also take time to know the patient. Within reason, they must come to know what the patient's feelings are and why. The following are some simple examples in which there might have been an improvement in the technic.

1. A desiring wife was sent into seventh heaven by being told that at long last she was pregnant. Her medical adviser had known for years how much her whole life was built around having a child. Nevertheless, two months later, with cold, precise, impersonal and scientific exactitude he informed her that hysterectomy was indicated and that she might as well put out of her mind the thought of having a child. The patient did not wait to have her hysterectomy before she had a frank emotional blow-up with suicidal implications.

In this instance, somebody forgot that patients are people.

2. Without having any special grudge against the gynecologists, I recall an instance in which medical students participated in an examination. With the patient on the table, they all examined her and speculated on the diagnostic possibilities, including malignancy, ectopic pregnancy, fibroid and a few other things. Then the woman was given a pat on the back and told to come back in three months to be examined again and to be told whether or not she had a malignant lesion. That was another instance in which an emotional explosion occurred and the psychiatrist was called in during the waiting period.

Here again, someone forgot that patients are people.

3. I wonder how common it is to forget the often devastating psychological effect of advising a woman that she should have a panhysterectomy and that she is not going to have any further use for these organs anyway because she is past the menopause. I wonder whether members of the opposite sex would not also suffer some psychological trauma if something similar were suggested just because their procreative faculties were no longer indispensable.

Women as well as men are people.

4. In the whole broad field of cardiovascular disease there is also the necessity for thinking of patients as people. Everyone knows the futility of frightening a cardiac patient by telling him first that he will have to go slow the rest of his life and that he will have to be prepared to meet his Maker at any time, then telling him to relax and take it easy. Such a prescription, of course, cannot be filled, even by the most phlegmatic.

No disease ever existed without the patient. The disease and the patient are found together. Patients are people. An astonishing job has been done in the technical side of treatment of disease. But the physician must never forget that disease is a mixture of which the personality is always a part.

CONCLUSION

Psychiatry as a part of medicine has experienced a material growth. It is taking cognizance of its responsibilities and is striving to bring its help within the reach of the multitude.

I repeat that in 1950 there is a conscientious, hardheaded, nonvocal psychiatry which deserves the confidence and respect of the public and the profession. It can contribute toward the advancement of the medical sciences, but it also avidly seeks scientific and clinical assistance from all medicine, of which it is a part.

Clinical Notes, Suggestions and New Instruments

ADRENOCORTICOTROPIC HORMONE

Its Successful Use in Keratitis in a Diabetic with Moderate Heart Disease

STEVEN A. MAZAR, M.D.
and
ROBERT M. BOGDASARIAN, M.D.
Binghamton, N. Y.

There have been several reports of the successful use of pituitary adrenocorticotropic hormone (ACTH) in ophthalmologic conditions.[1] We wish to report on its successful use in a case of severe and long-standing superficial disseminated keratitis of the punctate and coalescing type. This had failed to respond to the conventional antibiotic and supportive therapy during a nine month period. After 10 days of therapy with pituitary adrenocorticotropic hormone there was a fairly dramatic improvement that has been sustained for six months. The case is further interesting because the patient is severely diabetic, needing usually 65 units of insulin daily, and because she has severe arteriosclerotic heart disease, compensated only by continued digitalization and by the use of mercurial diuretics once or twice weekly during the past year. Thorn and his associates,[2] in an excellent review of the recent clinical applications of pituitary adrenocorticotropic hormone and cortisone therapy, state, "It appears that the use of ACTH is contraindicated in diabetes mellitus, congestive heart failure, hypertensive cardiovascular disease, Cushing's syndrome, acne, hirsutism, osteoporosis and osteomalacia.

Because of the protracted course and severity of the symptoms of keratitis in this patient and because of her deteriorating morale, she was hospitalized at the Binghamton City Hospital on May 1, 1950. Therapy with pituitary adrenocorticotropic hormone was ventured in spite of the relative difficulties, or perhaps even contraindications, engendered by both the severe diabetic state and the edema-electrolyte disturbances of her heart disease. The potentialities were discussed with the patient and family; the patient was desperate for relief.

REPORT OF A CASE

B. K., a white Jewish woman aged 59, was admitted to the hospital with the chief complaints referable to the right eye: severe pain, scratchy sensations, blurred vision and the entire eye greatly reddened. These had lasted for nine months and had been progressive, with short temporary partial remissions. She had been under the care of several ophthalmologists in succession.

Systemic Review.—Systemic review disclosed the following pertinent history: The patient had not had previous eye troubles; her vision had been good, with the usual refraction changes. She occasionally had left frontal sinusitis. Her hearing was normal. She was edentulous, but wore satisfactory plates. There was no history of unusual repiratory diseases, except for bronchopneumonia, for which she had been hospitalized three times during the period 1944 to 1946. In the past three years she had been hospitalized three additional times for congestive heart failure and twice for severe angina simulating coronary thrombosis. Electrocardiograms never confirmed a true infarction. She had a moderate amount of dyspnea on exertion, orthopnea, a frequent cough and mild peripheral ankle edema. Her cardiac status was fairly well controlled by a low salt diet. She was digitalized most of the time during the past three years, taking 0.2 mg. of digitoxin daily, although she had never been known to have fibrillation; she needed glyceryl trinitrate occasionally for angina. She had needed more and more frequent mercurial injections until half a year ago when she was instructed in self administration of mercaptomerin (thiomerin®) sodium, which she took in 1.0 cc. doses once or twice weekly, her weight and symptoms being her chief guide. In the past her blood pressure tended to be rather high, 160 to 190 systolic and 90 to 100 diastolic.

The patient's appetite was usually good. There was some fatty food intolerance, for which a cholecystectomy was performed in 1924. Ten years ago she weighed 190 pounds (96.2 Kg.). She successfully dieted to around 120 pounds (54.4 Kg.) four years ago, and since then she gradually lost weight to the present range of around 100 pounds (45.4 Kg.). She was habitually constipated and for this she took cascara sagrada pills, one to two every night. She had several drug idiosyncrasies, notably to codeine, and perhaps to morphine and pantopon® (a mixture of opium alkaloids). Whether given orally or parenterally, these caused episodes of severe gastritis.

The diabetes history dated back to 1928. The patient had been variably controlled so far as diet is concerned; strict cooperation from her usually was poor, as she had her own ideas about diet. Not surprisingly, the insulin requirement was gradually increased over the years. From the available records, it was seen that in 1937 she was on a schedule of 25 units of regular insulin (15-0-10); in 1943, 40 units of regular insulin (20-0-20); in 1945, 35 units of protamine zinc insulin and 25 units of regular insulin, given in the morning, and in 1947, 40 units of protamine zinc insulin and 35 of regular insulin. In 1949 she was rather well controlled on 60 units of insulin, 40 protamine zinc insulin and 20 regular insulin. In recent months she was well controlled on 55 units, 35 protamine zinc insulin and 20 regular insulin. Throughout all these years she had few minor insulin reactions and apparently never had been in severe acidosis or coma.

The patient had chronic recurring urinary symptoms dating back to 1919 when, while six months pregnant, cystoscopy was first done for acute urinary retention, apparently due to a stricture. In 1922, a cystotomy was performed for a bladder "stone." In 1941 she had a thorough genitourinary work-up; a meatotomy was done for a urethral stricture, and a urethral caruncle was studied by biopsy and removed by fulguration. She continued to have urinary symptoms for which she had numerous urethral dilations, and several more cystoscopic and pyelographic examinations. However, no gross abnormalities were found. She continued to have a low grade urinary sepsis, manifest by a persistent pyuria with an occasional typical pyelitis attack on the left side. Antibiotics effected temporary ameliorations. She had a myomectomy in 1924 and a hysterectomy in 1926 at the age of 35, with minor and transient menopausal symptoms in their due course.

The patient was an individualist and had her own way in most things, sometimes, unfortunately, even in her medical management. She was despondent at times, expressing thoughts of suicide. Hospital diets were seldom to her liking, and she always insisted on her own selections. However, she was a good worker and managed household duties mostly by herself, a few times unwisely driving herself into cardiac decompensation necessitating hospitalization.

Summary of Past History.—The patient had undergone a cystotomy in 1922, a cholecystectomy in 1924, a myomectomy in 1924 and a hysterectomy in 1926. She had had diabetes mellitus since 1928. A tonsillectomy was performed in 1931. She had had pneumonia three times during the period 1944 to 1946. Numerous cystoscopic examinations had been made since 1919. She had had several acute pyelitis attacks since 1940 and arteriosclerotic heart disease with active symptoms since 1945.

Physical Examination.—The patient was a well developed but poorly nourished woman aged 58, in moderate distress with her right eye. Her left eye was normal. The entire globe and conjunctiva of the right eye were intensely injected; the cornea was opalescent and edematous, and the pupil was widely dilated with atropine. The intraocular tension was within normal limits by palpation. The ears, the nose and the throat were normal except

---

From the Memorial Building, Binghamton City Hospital.

1. Gordon, D. M., and McLean, J. M.: Effects of Pituitary Adrenocorticotropic Hormone (ACTH) Therapy in Ophthalmologic Conditions, J. A. M. A. **142**:1271 (April 22) 1950. Olson, J. A.; Staffensen, E. H.; Margulis, R. R.; Smith, R. W., and Whitney, E. L.: Effect of ACTH on Certain Inflammatory Diseases of Eye, J. A. M. A. **142**:1276 (April 22) 1950. Mann, W. A., and Markson, D. E.: Case of Recurrent Iritis and Episcleritis on Rheumatic Basis Treated with ACTH, Am. J. Ophth. **33**:459 (March) 1950.

2. (*a*) Thorn, G. W., and others: Medical Progress: The Clinical Usefulness of ACTH and Cortisone, New England J. Med. **242**:783 (May 18) 1950; (*b*) ibid. **242**: 824 (May 25) 1950; (*c*) ibid. **242**: 865 (June 1) 1950.

for a left frontal sinusotomy scar and an edentulous mouth with suitable dentures. Examination of the neck revealed no increased venous distention and no palpable thyroid gland. The chest was emphysematous, and the breasts were normal. The lungs were clear. The heart was not clinically enlarged, there was normal sinus rhythm, the heart sounds were of good quality with accentuation of the aortic second sound, and there were no murmurs. The blood pressure was 155/75 bilaterally. On her abdomen there were three large operative scars. The liver edge was palpable just below the costal margin and tender. Neither spleen nor abdominal masses were palpable. The skin over the abdomen had a peculiar doughy nondependent edema, with a very slow filling of any pitted areas, and the breasts were similarly edematous.

There was edema (1 plus) in the ankles and also minimally in the sacrum, with the same pitting quality mentioned above. Neither cyanosis nor varicose veins were observed. The results of the neurological and rectal examinations were negative.

adrenal glands. We were not prepared to do any 17-ketosteroid urine studies for otherwise demonstrating the effectiveness of our pituitary adrenocorticotropic hormone therapy; hence we continued on clinical grounds alone.

Drug Schedule.—The pituitary adrenocorticotropic hormone was provided in 20 mg. and 10 mg. individual vials with contents dissolved always just prior to the intramuscular injection. Doses were given three times a day at six hour intervals, with night doses omitted. The patient received 60 mg. of the drug in three divided doses on the first day, after which (but coincidental with which, we are sure) anorexia developed; she vomited numerous times for the next few days. Because this disrupted the basal state, difficult at best with the diabetes and the maintenance of cardiac compensation, and because of the patient's anxiety, use of the drug was discontinued and resumed in a week after conditions stabilized again. This time the patient again received 60 mg. of pituitary adrenocorticotropic hormone daily for the first two days (20 mg. three times a day), then 30 mg. of pituitary adreno-

Clinical and Laboratory Data

Day in Hospital	Blood Electrolytes, Mg./100 Cc.	Nonprotein Nitrogen, Mg./100 Cc.	Blood Sugar, Mg./100 Cc.	CO_2-Combining Power, Vol. %	Leukocyte Count: Total	E., %	M., %	L., %	P. M. N., %	Blood Pressure	Weight, Lb.	Urine Sugar Profile	Therapy: ACTH, Mg. Daily	Therapy: Insulin, Units Daily
1	.....	34	260	41	5,150	1	..	39	60	170/80	94	.....	..	55
2	.....	..	...	..	.....	..	..	..	..	.....	..	.....	..	55
3	.....	..	...	..	.....	..	..	..	..	.....	..	.....	..	55
4	.....	41	140	58	.....	..	..	..	..	.....	93½	1111	..	55
5	250 —Na 22 —K 425 —Cl	..	...	..	5,350 6,250	00 00	13 3	20 34	51 63	155/75	..	13344	60	65
6	.....	..	154	58	7,700	00	4	51	45	.....	93½	12444	..	65
7	.....	..	...	..	.....	..	..	..	..	165/70	..	113131	..	65
8	.....	30	157	62	6,200	00	16	43	41	.....	96	11111	..	65
9	.....	..	...	..	.....	..	..	..	..	150/70	..	102122	..	55
10	.....	..	...	..	.....	..	..	..	..	.....	97	111000	..	55
11	.....	..	...	..	.....	..	..	..	..	145/70	..	100001	..	55
12	.....	..	...	..	7,000	00	7	46	47	.....	100	100010	60	55
13	.....	..	...	..	.....	..	..	..	..	120/65	..	443444	60	75
14	.....	..	...	..	.....	..	..	..	..	.....	102	310023	30	65
15	.....	..	...	..	8,750	00	..	56	44	118/60	..	101	30	65
16	21 —K	..	118	60	.....	..	..	..	..	.....	101	122100	20	65
17	.....	..	...	..	.....	..	..	..	..	135/65	..	110010	20	65
18	.....	..	...	..	.....	..	..	..	..	.....	100	02012	20	65
19	.....	..	...	..	.....	..	..	..	..	120/70	..	101110	20	65
20	.....	..	...	..	.....	..	..	..	..	.....	102	111111	20	65
21	.....	..	...	..	.....	..	..	..	..	.....	..	002111	20	65

Course in Hospital.—Preliminary laboratory studies were done for the necessary controls. These are incorporated in the table. A chest roentgenogram revealed normal lung fields and an aortic type heart with a prominent knob. An electrocardiogram revealed normal sinus rhythm, left axis deviation and digitalis effect, all similar to those of her previous graphs. A drop in the total circulating eosinophils is one of the most valuable guides to control of adequate therapy, but this failed when the pretreatment eosinophil count was reported as zero, as were all other eosinophil counts during therapy and one month afterwards. This is an unexplained phenomenon, peculiar to this patient we believe, because concurrent tests were being done regularly on other patients, with the expected average eosinophil counts. An initial white blood cell count was 5,150 with 60 per cent polymorphonuclear leukocytes, 39 per cent lymphocytes and 1 per cent eosinophils. This was from the usual Wright's stain blood smear. This was done at another laboratory. It is interesting that from her 13 previous available hospitalization records over the past 10 years there were never any eosinophils reported, and on two occasions two years apart during supposedly viral pneumonitis, there was leukopenia. The white blood cell count was 3,450, with 60 per cent polymorphonuclear leukocytes, 36 per cent lymphocytes, and 4 per cent mononuclear leukocytes; another count was 3,300, with 63 per cent polymorphonuclears and 37 per cent lymphocytes. We might speculate that the stress of hospitalization and anxiety over the new, expensive and potentially hazardous medicine were effective pretherapy stimuli to our patient's corticotropic hormone for the following two days (10 mg. three times a day), then 20 mg. a day for an additional six days (10 mg. twice a day), making a total of 360 mg. On the day following the initial trial of 60 mg., the eye was improved, there was less ciliary injection and the pain was considerably less. The eye continued in its improvement for three days, even while the general clinical picture was deteriorating because of nausea and vomiting and the need for parenteral alimentation. Thereafter, the eye symptoms and findings increased again. When the course of pituitary adrenocorticotropic hormone was resumed, we again noted a significant improvement in the eye within 24 hours; the cornea became clearer, and the ciliary injection decreased. After five days of regular but diminishing amounts of the drug the eye was described as white, though there was minimal ciliary injection at the equators. The cornea was clear, and the patient was pain free.

CLINICAL CONSIDERATIONS

There was considerable euphoria, probably chiefly because of relief from the intractable symptoms of the previous nine months. The patient volunteered that she was ravenously hungry during the course of therapy. She usually experienced a dull headache about half an hour after each of the intramuscular injections. There was a gradual increase in weight from the 93½ pounds (42.43 Kg.) initially to the 102 pounds (43.6 Kg.) on discharge 18 days later, although there was no visible increase in the peculiar edema mentioned above, and perhaps even a decrease. The patient received her mercurial, mercaptomerin (thiomerin®)

sodium, 1.0 cc. every other day, during her hospital stay, whereas her previous requirement at home was twice a week. It was felt desirable to keep her rather dehydrated because of the counterbalancing water retention effect of the pituitary adrenocorticotropic hormone. Some risk is reported to attend this, but the patient was watched for signs of undue fatigue and muscular weakness. Potassium citrate, 15 grains (0.97 Gm.) four times daily, was given one day because of suggestive symptoms. Mecurial diuresis induces a large renal loss of potassium, and Thorn and his co-workers [2] mention it as a contraindication during therapy with pituitary adrenocorticotropic hormone, unless full doses of potassium chloride are being given simultaneously. They mention 1 or 2 Gm. of enteric-coated potassium chloride three times daily.

The initial carbon dioxide-combining power was 41 volumes per cent, and when the determination was repeated just prior to therapy it was 58 volumes per cent. The other two readings were 62 volumes per cent and 60 volumes per cent during pituitary adrenocorticotropic hormone therapy. These are not striking except that in previous hospitalizations, primarily for nondiabetic reasons, the patient's better carbon dioxide-combining powers were usually in the range of 50 to 55 volumes per cent when she was apparently fairly well controlled. The expected physiological effect of pituitary adrenocorticotropic hormone on electrolyte balance is to produce a hypokalemic, hypochloremic alkalosis, and our chemistry studies deviated in that way. The insulin doses given were 10 to 20 units higher once pituitary adrenocorticotropic hormone was started, but the patient was also eating better. It is difficult to say whether this represents a true increased insulin requirement or merely closer and better control. Thorn and his co-workers [2] mention that patients with preexisting diabetes will have their diabetes markedly aggravated by pituitary adrenocorticotropic hormone or cortisone therapy. This was not our experience. All urines were tested for sugar, and a useful means of recording it was designated as a urine sugar profile. For example, on the customary zero to 4 plus basis, if the patient had eight urine specimens in 24 hours, the profile might be read as 31002322. This number shows at a glance the extent of diabetes control as manifest by urine sugar over a 24-hour period. Elkinton and his associates [3] noted in nondiabetic persons a slight glycosuria in three of seven cases on the days when moderate doses of pituitary adrenocorticotropic hormone were given. This glycosuria was associated with slightly increased blood sugar values. The values all reverted to normal when therapy was stopped. Conn, Louis and Johnston [4] noted severe glycosuria after therapy with pituitary adrenocorticotropic hormone, and had convincing evidence that a true diabetic state would develop on long-continued use of the drug in adequate doses. However, Conn and his co-workers also have evidence that the renal threshold for glucose was lowered, making some of this glycosuria renal.

The daily blood pressures varied from 155/75 to 120/70, with the lower levels toward the end of the treatment rather than the other way around. Others have occasionally noted a blood pressure increase during therapy. It may well be that potential hypertension may be brought to light (Sprague [5]).

COMMENT

This represents an initial use of the pituitary adrenocorticotropic hormone by us, and it posed more than the average problems reported in other cases: mainly the severe diabetes, the mercurial-sustained compensation of an arteriosclerotic heart, and the absence of demonstrable eosinophils in the peripheral blood, with consequent loss of a most valuable yardstick by which adrenocortical response is measured. Following the clinical experience of others as far as dosage and methods were concerned and adapting it to our patient, we were able safely to effect a therapeutic response *sine qua non*.

It is well to have a definite plan in mind when initiating a course of pituitary adrenocorticotropic hormone or cortisone therapy, and from our experience in this case and from experiences reviewed in recent literature, the following are effective yet simple guides to therapy control: It is necessary to have conditions stable and basal as nearly as possible, or there will occur too many variables that confuse evaluations. It might be desirable in some cases to begin with saline blank injections for a day or so to test the patient's psychological responsiveness; then unbeknown to the patient and perhaps even the nursing and house staff, the therapy with pituitary adrenocorticotropic hormone should be started, using total circulating eosinophil counts periodically to demonstrate the desired eosinopenia. Lymphopenia, polymorphonuclear leukocytosis, and reticulocytosis are other physiological effects demonstrable by blood cell counts. In our case the total white blood cell count rose slightly but definitely; however, there was no lymphopenia. A daily weight record and an accurate fluid intake and output record will reflect any significant water and salt retention potentials of these drugs. A patient with borderline cardiorenal disease is liable to be pushed into an edema phase quite readily. These data will be a guide to any salt restriction therapy. Daily determinations of urine sugars are easy to do and potentially valuable. Though the reports of steroid diabetes are rare, nevertheless, potential diabetes might well be brought to light, as suggested by Thorn.[2a] An initial fasting blood sugar determination is desirable as a base line for any future repeat blood sugar determinations. Blood pressure determinations once or twice daily are similarly potentially valuable, although here again, though a true hypertension may not be really created, an existing hypertension may be aggravated. Electrolyte studies are desirable during the therapy when signs or symptoms are suggestive, for example, the muscle weakness of hypopotassemia or the asthenia of adrenocortical exhaustion from overstimulation with pituitary adrenocorticotropic hormone. It is undesirable to stop a course of therapy abruptly, and the present trend is to taper off gradually with diminishing doses to prevent a sudden collapse of adrenocortical function. It is necessary to bear in mind the adverse effects of the drugs on healing of wounds; Ragan and his co-workers [6] first noted this when biopsy wounds in patients with rheumatoid arthritis treated with cortisone were slow to heal.

Pituitary adrenocorticotropic hormone and cortisone have such a vast therapeutic spectrum that it is well to observe all the benefits or ill effects that the patient derives, subjectively and objectively, and not just those pertinent to the initial reasons for the therapy. Sprague and his associates [5] present a very comprehensive review of their observations on the physiological effects of cortisone and pituitary adrenocorticotropic hormone in man. Many of these physiological effects may bear evaluation in each patient, development or increase of acne, hirsutism, moon facies and delayed menses in women. Gout can be precipitated by therapy with pituitary adrenocorticotropic hormone, as well as treated by it. Myasthenia gravis can initially be seriously worsened by the therapy, before any subsequent benefit is noted.[7] Euphoria or mental depression may develop, especially after prolonged therapy.

SUMMARY

A case of severe keratitis of nine months' duration, unresponsive to the usual therapies, was promptly and successfully treated with pituitary adrenocorticotropic hormone (ACTH) in a total dosage of 360 mg., over a 10-day treatment period.

The treatment was complicated by the fact that the patient was severely diabetic, requiring 65 units of insulin daily, and had moderately severe cardiac disease, requiring biweekly mercurials for compensation.

The diabetes was not particularly aggravated, nor was the state of compensation too difficult to maintain.

The patient has not had a relapse after six months of a clinical cure of the keratitis.

3. Elkinton, J. R., and others: Effects of Pituitary Adrenocorticotropic Hormone (ACTH) Therapy, J. A. M. A. **141**:1273 (Dec. 31) 1949.

4. Conn, J. W.; Louis, L. H., and Johnston, M. W.: Metabolism of Uric Acid, Glutathione and Nitrogen, and Excretion of "11-Oxysteroids" and 17-Ketosteroids During Induction of Diabetes in Man with Pituitary Adrenocorticotropic Hormone, J. Lab & Clin. Med. **34**: 255 (Feb.) 1949.

5. Sprague, R. G., and others: Observations on the Physiologic Effects of Cortisone and ACTH in Man, Arch. Int. Med. **85**: 199 (Feb.) 1950.

6. Ragan, C.; Grokoest, A. W., and Boots, R. H.: Effects of Adrenocorticotropic Hormone (ACTH) on Rheumatoid Arthritis, Am. J. Med. **7**: 741 (Dec.) 1949.

7. Proceedings of the First Clinical ACTH Conference, Philadelphia, The Blakiston Company, 1950, pp. 127, 529 and 584.

THERAPEUTIC EFFECT OF PITUITARY ADRENOCORTICOTROPIC HORMONE (ACTH) IN A CASE OF HENOCH-SCHÖNLEIN VASCULAR (ANAPHYLACTOID) PURPURA

MARIO STEFANINI, M.D.
CHARLES A. ROY, M.D.
LEDA ZANNOS, M.D.
and
WILLIAM DAMESHEK, M.D.
Boston

Increasing attention has recently been focused on a group of conditions characterized by a widespread alteration of the collagenous tissue. Active vasculitis of various regions appears to be, among other characteristics, a fairly constant common denominator in this group of diseases which includes such heterogeneous conditions as disseminated lupus erythematosus, acute glomerulonephritis, polyarteritis nodosa and serum sickness. Some of these conditions have a possible allergic causation, while in others the pathogenetic mechanism is obscure. Recently an additional characteristic has come to the fore, i. e., a variably favorable response to treatment with anterior pituitary adrenocorticotropic hormone (ACTH).[1]

Fig. 1.—Microscopic appearance of a section of skin before pituitary adrenocorticotropic hormone therapy. Active inflammatory reaction centered around the small vessels and capillaries, which appear destroyed in some areas (× 110).

The nonthrombopenic Henoch-Schönlein type of vascular or anaphylactoid purpura is another condition which may be related to this group in view of its possible allergic basis and its severe generalized vasculitis. The classic capillary lesions are represented by active inflammatory changes centered around the smallest vessels with infiltration of inflammatory cells, and destruction and dilatation of capillaries. Edema of the epidermis and corium may also be present in the affected areas.

Because of these considerations we thought it of interest to observe the effects of treatment with pituitary adrenocorticotropic hormone in a case of severe vascular anaphylactoid purpura of the nonthrombopenic type, with associated glomerular involvement.

REPORT OF CASE

D. F., a boy aged 3 years, was admitted to the Boston Floating Hospital on Feb. 24, 1950. The family and past history were noncontributory. During the last week of January 1950 the patient had on his face a few red pin-point spots which disappeared in a few hours. At the same time, he experienced pain and difficulty in walking and his parents noticed moderate swelling and tenderness of both his ankles for a day or two. On Feb. 6, 1950 many purpuric lesions were noticed on the extremities and buttocks. On his admission to another hospital the following observations were recorded: The temperature was 100 F. rectally; purpuric dark red spots, not disappearing with pressure, were seen over extremities, face, hypogastrium and genitalia; the tonsils were moderately enlarged and infected, there was acute otitis media of the right side, and the ankles were moderately swollen. A diagnosis of meningococcemia was considered, and sulfadiazine was given for five days, when it was discontinued because of gastric intolerance and the appearance of acetylsulfadiazine crystals in the urine. Laboratory examinations revealed a Streptococcus viridans in the throat culture; blood cultures were negative for Meningococcus, Typhus and Brucella. The bone marrow and peripheral blood appeared normal. Clotting, bleeding and prothrombin times were also within normal limits. Occult blood was found in the stools and vomitus.

On February 20, while the previous skin lesions were fading away, a new hemorrhagic rash appeared, large and confluent, involving all the extremities. Edema of the face, headache and cramplike abdominal pain at irregular intervals presented themselves at the same time. On February 23 about 1 teaspoon of red blood was passed with a bowel movement. The patient was then referred to the Boston Floating Hospital for further study. On examination the child complained of intermittent severe abdominal pain. He appeared rather pale. The skin over the extremities, buttocks and face was covered with purpuric spots varying in size and shape and mostly located on the extensor surfaces. Some of the lesions were elevated and some were excoriated as the result of scratching. Other positive observations included a grade 2 systolic murmur heard best in the third and fourth left intercostal space and transmitted over the entire precordium, the liver edge palpable 1 fingerbreadth below the costal margin and moderate swelling of the left ankle. The abdomen was tender without rigidity. Swab culture of the throat again revealed Strep. viridans and a nonhemolytic Streptococcus. Blood examination disclosed a moderate grade of anemia (red blood cells 3,120,000; hemoglobin 60 per cent) and normal leukocytes: there were 7,500 white blood cells, with a differential count of polymorphonuclear leukocytes 45 per cent, lymphocytes 37 per cent, monocytes 15 per cent, basophils 1 per cent and eosinophils 2 per cent; there was a normal platelet level and a normal bone marrow. The sedimentation rate (Westergren) was 11 mm. in one hour. Examination of the urine revealed faint traces of albumin, and the sediment showed 15 red blood cells and four white blood cells per high power field.

Tests for study of the hemostatic mechanism gave the following results: platelets, 380,000 per cubic millimeter; bleeding time, 3½ minutes; tourniquet test, negative; clotting time, 5 minutes; prothrombin activity, 100 per cent; labile factor activity, 100 per cent; clot retraction, normal; prothrombin activity of serum, 8 per cent (one hour after completion of coagulation), and serum/plasma prothrombin activity ratio, 8.0. No fibrinolysis was evident after 48 hours of incubation of the clot at 37 C. There was no demonstrable anticoagulant. In the tourniquet test 22 petechiae appeared in an area 1 inch in diameter after application of infradiastolic pressure for 10 minutes.

This work was supported in part by grants from the C. H. Hood Dairy Foundation and the American Cancer Society, Massachusetts Division.

This work was completed during the tenure of a Damon Runyon Clinical Research Fellowship (Dr. Stefanini) administered by the American Cancer Society.

From the Ziskind Laboratories (Hematology Section) of the Joseph H. Pratt and New England Center Hospitals, the Boston Floating Hospital and the Departments of Medicine and Pediatrics, Tufts College Medical School.

Dr. James Marvin Baty, professor of pediatrics, Tufts College Medical School, and physician in chief, Boston Floating Hospital, enabled us to study this case. Dr. H. Edward Mac Mahon, professor of pathology and bacteriology, Tufts College Medical School, interpreted the microscopic sections.

1. Thorn, G. W., and others: Medical Progress: The Clinical Usefulness of ACTH and Cortisone, New England J. Med. 242:783-793 (May) 1950.

Occult blood was detected in the stools. The nonprotein nitrogen level of the blood was 22 mg. per 100 cc. Roentgenograms of the long bones and chest showed no abnormalities. Lumbar puncture revealed clear fluid under normal pressure; the total protein was 9.2 mg., sugar 84 mg. and chlorides 708 mg., per 100 cc., and a culture was negative.

Fig. 2.—Photograph of the patient at the beginning of pituitary adrenocorticotropic hormone therapy.

The patient was kept under observation and given penicillin, 300,000 Oxford units a day. The purpuric rash slowly cleared; by the sixteenth hospital day it had almost completely disappeared. The stools were still positive for blood, and the child had intermittent severe abdominal pains. Daily urinalysis continued to show moderate albuminuria, presence of red and white blood cells in the sediment and, at times, coarse granular casts.

On the fifteenth hospital day the petecchial rash reappeared with the same intensity as on admission. The patient was then given aureomycin hydrochloride, 100 mg. every four hours. After six days of such treatment without improvement of the

Fig. 3.—Photograph of the patient at the suspension of therapy. Note the residual pigmentation in areas that previously had hemorrhagic lesions. Only a few new petechiae are present.

child, whose abdominal pains became more frequent and severe, pituitary adrenocorticotropic hormone therapy was started in a dosage of 5 mg. given three times a day subcutaneously. This preparation was supplied by Dr. E. B. Astwood and is a glacial acetic acid extract derived from pork pituitary gland.[2] At this time a skin biopsy was made. The specimen consisted of an elliptical piece of skin with a subcutaneous depth of 0.6 cm. The most striking change was the exceedingly active inflammatory reaction centered about the small vessels or capillaries, especially in the superficial layer of the corium. Capillaries were destroyed in some areas, dilated in others. This type of inflammatory reaction accompanied by hemorrhage is consistent with Henoch-Schönlein purpura but may also appear in other peripheral vascular diseases showing acute reactive inflammatory changes (fig. 1). The appearance of the skin of the patient at the beginning of hormone therapy is indicated in figure 2.

Treatment with pituitary adrenocorticotropic hormone was continued for fourteen days, and a total of 210 mg. was administered together with a low salt diet. A total gain in weight of 3 pounds (1.3 Kg.) was noticed, but the blood pressure remained within normal limits throughout the entire course of therapy. The cutaneous lesions improved rapidly and almost completely disappeared after six days of treatment (fig. 3). Abdominal pains subsided early during therapy. The urine

Fig. 4.—Microscopic appearance of a section of skin taken immediately after suspension of pituitary adrenocorticotropic hormone therapy. The section was taken in an area of fresh hemorrhage; hence, most of the infiltrating cells are erythrocytes and the perivascular lymphocytic infiltration is minimal (× 110).

also became more nearly normal, as the albuminuria diminished and casts were no longer observed in the sediment. The personality of the child was strikingly affected; although on admission he had appeared shy and withdrawn, he later became active and even aggressive. At the time of suspension of therapy a second skin biopsy taken in the only area of fresh hemorrhage showed massive hemorrhage into the corium and underlying tissue. The epidermis was intact. The active inflammatory disturbance previously noted had almost completely disappeared, and the reticular layer of the corium now showed the most minimal perivascular lymphocytic infiltration. The skin appendages were not affected (fig. 4).

Six days after pituitary adrenocorticotropic hormone therapy was discontinued new small purpuric lesions reappeared on the lower extremities and mild abdominal pains also recurred. Both symptoms receded promptly, and one month after discontinuing hormone therapy (April 19, 1950) the patient was discharged asymptomatic. The urine, however, again showed 0.5

2. Astwood, E. B.; Cleroux, A. P.; Payne, R. W., and Raben, M. A.: Therapeutic Studies on Some Newer Corticotrophic (ACTH) preparations, Bull. New England M. Center 12: 2-10 (Feb.) 1950.

per cent of albumin and a few granular casts in the sediment besides red cells and white cells, which had never disappeared altogether even during therapy.

After his return home the patient felt well, gained some weight and played actively. He was readmitted one month later (May 15, 1950). Sixteen hours before admission, he had felt feverish and complained of headache and weakness in his legs. The next morning he had passed port-wine-colored and smoky urine. At examination the temperature was 103.4 F. and the blood pressure 100/60. A few purpuric spots were noted on both cheeks. Laboratory examinations showed reddish urine that contained albumin (0.5 per cent); red blood cells (80 per field) and white blood cells (4 per field), and a few fine granular casts. The nonprotein nitrogen level was 48 mg. per 100 cc. Blood examination revealed a mild hypochromic anemia. Penicillin 50,000 units every four hours was given, and the temperature quickly fell to normal. Four days after admission a few purpuric spots were noted on the ankles, legs and elbows. They faded the following day. At no time did the patient complain of abdominal pain, nor was occult blood detected in the stools during this admission. Throat culture again revealed Streptococcus viridans.

Effect of Pituitary Adrenocorticotropic Hormone (ACTH) Therapy on the Urinary Findings in a Case of Anaphylactoid Purpura with Glomerular Involvement

Days After Start of Therapy *	R. B. C. Per Field	W. B. C. Per Field	Albumin Percentage	Casts † Per Field
0	16	12	0.5	1.2
5	16	10	0.2	3.0
11	40	15	0.2	0
15	15	14	0.05	0
30	18	5	0.5	0.5
45	15	9	0.5	0
75	60	4	0.5	0.4
120	20	9	0.3	0.6

* Therapy was suspended on the fifteenth day.
† Casts were mostly fine, of the granular and epithelial type.

Phenolsulfonphthalein elimination was normal; intravenous pyelography failed to show any abnormality. The serum protein level was 6.5 Gm. per 100 cc. (albumin 3.6 Gm. and globulin 2.6 Gm.).

Since then, the patient has remained in good condition. The urine appears normal in color and specific gravity, but a small amount of albumin is still present, as are red and white blood cells and a few casts in the sediment. At the time of writing (four months after the cessation of therapy) the patient enjoys perfect health, but the urinary findings are still unchanged. A nonprotein nitrogen determination gives a value of 31 mg. per 100 cc.

COMMENT

The diagnosis of Henoch-Schönlein nonthrombopenic purpura in this case seems to be fairly certain, in the light of the following rather characteristic clinical and laboratory observations: (*a*) the sudden occurrence and frequent recurrence of purpuric manifestations; (*b*) the association of the purpura with melena and hematuria, indicating the involvement by the vasculitic process of intestinal tract and kidney; (*c*) the articular symptoms early in the course of the condition, and (*d*) the laboratory results, showing increased capillary fragility but a normal mechanism of blood coagulation and normal bleeding time in a subject with purpura.

Several therapeutic agents have been suggested from time to time for the treatment of anaphylactoid purpura. Citrin (vitamin P; hesperidin), ascorbic acid, rutin and antihistamine drugs have been recommended and have given good, and sometimes spectacular, results in individual cases. The evaluation of any therapeutic procedure in this disease is difficult, however, because the disease presents frequent spontaneous remissions.

The same limitation applies to the evaluation of pituitary adrenocorticotropic hormone therapy in our case. As often happens with this disease, antibiotic therapy failed to modify the condition. On the other hand, treatment with the hormone agent undoubtedly influenced the process at least to some extent. The disappearance of abdominal symptoms was prompt and striking, and the skin lesions faded early during therapy. Skin biopsies taken in two areas of fresh hemorrhage at the beginning and at the end of therapy indicated a striking regression of the vasculitic changes. However, the hormone did not eradicate the disease. Small numbers of petechiae appeared even during therapy; purpuric spots and abdominal symptoms recurred temporarily after the suspension of treatment. The renal manifestations of the disease were only temporarily improved (see the accompanying table), and the establishment of a chronic nephritic process, a common occurrence in anaphylactoid purpura, was not prevented by pituitary adrenocorticotropic hormone therapy.

Particularly remarkable was the change in personality of the patient, who was shy and introverted before his disease and at the time of admission but became extroverted and aggressive shortly after the suspension of hormone therapy. After his discharge from the hospital the patient soon reverted to his withdrawn attitude.

SUMMARY

A case of severe anaphylactoid p[illegible]ura of the nonthrombopenic Henoch-Schönlein-type with glomerular involvement in a child 3 years of age was treated with pituitary adrenocorticotropic hormone (ACTH), with the following results:

(*a*) The treatment was followed by striking regression of the vasculitic changes characteristic of the disease. The abdominal symptoms were promptly relieved and the cutaneous hemorrhagic manifestations diminished quickly.

(*b*) Mild abdominal symptoms and petechial manifestations reappeared after the suspension of the therapy but regressed spontaneously in a short time.

(*c*) The signs of renal involvement were only temporarily affected by hormone therapy, which did not prevent the establishment of a mild chronic glomerulonephritis.

(*d*) Remarkable changes in the personality of the patient were observed; these regressed shortly after the suspension of therapy.

Council on Foods and Nutrition

ACCEPTED FOODS

The following products have been accepted as conforming to the rules of the Council.

JAMES R. WILSON, M.D., *Secretary.*

Clapp's Baby Food Division, American Home Foods, Inc., Rochester, N. Y.

CLAPP'S STRAINED SWEET POTATOES. Ingredients: Sweet potatoes, malt syrup, salt and water necessary for preparation.

Analysis (submitted by manufacturer).—Total solids 15.97%, moisture 84.03%, ash 0.99%, fat (ether extract) 0.04%, protein (N × 6.25) 0.93%, crude fiber 0.51%, carbohydrates other than crude fiber (by difference) 13.82%.

Vitamins and Minerals	Mg./100 Gm.
Carotene	2.03
Thiamine	0.024
Riboflavin	0.072
Ascorbic acid	2.55
Nicotinic acid	0.385
Calcium	14.80
Phosphorus	40.20
Iron	0.72
Copper	0.38

Calories.—0.57 per gram; 16.28 per ounce.

Use.—For use in the feeding of infants, convalescents and others requiring a soft diet.

The Gerber Products Company, Fremont, Mich.

GERBER'S READY TO SERVE RICE CEREAL. Ingredients: rice flour, invert sugar syrup, dicalcium phosphate, rice bran oil, salt, water extract of rice bran, sodium iron pyrophosphate, nicotinamide, thiamine hydrochloride, and riboflavin.

Analysis (submitted by manufacturer).—Total solids 95.2%, moisture 4.8%, ash (minerals) 3.9%, fat (acid hydrolysis) 5.5%, protein (N × 6.25) 5.1%, crude fiber 0.3%, carbohydrates other than crude fiber (by difference) 80.4%.

Vitamins and Minerals	Mg./100 Gm.
Thiamine	6.88
Riboflavin	0.88
Nicotinic acid	6.9
Calcium	605
Phosphorus	680
Iron	70

Calories.—3.90 per gram; 111 per ounce.

Use.—For use in the feeding of infants and young children.

Council on Physical Medicine and Rehabilitation

REPORT OF THE COUNCIL

The Council on Physical Medicine and Rehabilitation has authorized publication of the following reports.

HOWARD A. CARTER, *Secretary.*

SILVERTONE HEARING AID, MODEL P-15, ACCEPTED

Manufacturer: W. E. Johnston Manufacturing Company, 708 West 40th Street, Minneapolis.

Distributor: Sears, Roebuck & Company, 925 South Homan Avenue, Chicago 7.

Silvertone Hearing Aid Model P-15

The Silvertone Hearing Aid, Model P-15, is an electric device recommended for the rehabilitation of the hard-of-hearing. Without the clothing clips, the case measures 85 by 58 by 21 mm. The weight of the instrument without batteries is 83 Gm. Receiver and cord weigh 11.5 Gm. and batteries 47.5 Gm., so that the total weight is 142 Gm. The Council's investigation showed that the instrument performed as represented by the manufacturer and that it met the requirements for acceptance. The Council on Physical Medicine and Rehabilitation voted to include the Silvertone Hearing Aid, Model P-15, in its list of accepted devices.

MICROTONE ADC AUDIOMETER, MODEL 53-C1, ACCEPTED

Manufacturer: The Microtone Company, Ford Parkway on the Mississippi, St. Paul 1.

The Microtone ADC Audiometer, Model 53-C1, is a portable instrument for testing a patient's hearing. It requires a source of 100 to 130 volt alternating current, being equipped to compensate for variations of line-voltage within this range. It is a pure tone audiometer and is equipped with both bone conduction and air conduction receivers. There is a microphone for communication with the patient during tests. Evidence obtained from a source acceptable to the Council indicated that this apparatus satisfies the Council's minimum requirements for the acceptance of audiometers. The Council on Physical Medicine and Rehabilitation voted to include the Microtone ADC Audiometer, Model 53-C1, in its list of accepted devices.

Microtone ADC Portable Audiometer, Model 53-C1

NATIONAL HEARING AID, ULTRATHIN MODEL 504, ACCEPTED

Manufacturer: National Hearing Aid Laboratories, 815 South Hill Street, Los Angeles 14.

The National Hearing Aid, Ultrathin Model 504, is an electric device recommended for the rehabilitation of the hard-of-hearing. With the exclusion of the clothing clips at the side, the case measures 114 by 60 by 24 mm. (tapering to 20 mm.), and the transmitter unit, without batteries, receiver cord and receiver, weighs 110.5 Gm. With batteries, receiver cord and receiver, the hearing aid weighs 170.5 Gm. It requires the usual zinc-carbon A and B batteries.

The Council's test of the instrument showed that it met the requirements for acceptance and that the performance, construction and material were as represented by the firm. The Council on Physical Medicine and Rehabilitation voted to include the National Hearing Aid, Ultrathin Model 504, in its list of accepted devices.

BROCKMAN THERAPEUTIC EXERCISER ACCEPTED

Manufacturer: Brockman Manufacturing Company, 25 Rockhill Road, Bala-Cynwyd, Pa.

The Brockman Therapeutic Exerciser is designed for giving active and passive exercise to patients. It resembles a bicycle in having a seat, handle bars and pedals. The rate of pedaling is governed by an electronic control housed in a cabinet, and the power is furnished by a motor which requires a source of 60-cycle alternating current at 110 volts and consumes 330 watts of power. The leather-covered adjustable seat is stationary, providing security for the patient. There are graduation marks for the seat level adjustment, the handle adjustments and the pedal arms. The reach to the handles provides variations for adapting the exerciser to both children and adults. After the initial adjustments these readings can be recorded on the patient's chart and the apparatus set for each individual patient.

Brockman Therapeutic Exerciser.

When the apparatus is used for active exercise, increments of resistance may be added by means of an electronic control. When it is used for passive exercise, the speed may be varied from slow to brisk activity; the movements of the pedals can also be reversed. The ankle can be placed either in front of or behind the axis of the pedal, so that the work can be distributed among the flexors and extensors of the ankle at will. Most patients find that they can get on and off the apparatus without aid.

Essential Measurements

	Height		Width		Length		Weight	
	Cm.	In.	Cm.	In.	Cm.	In.	Kg.	Lbs.
Therapeutic exerciser								
Unpacked	81	32	40	18	107	42	64	140
Crated *	92	36	61	24	122	48	120	265
Electronic control cabinet								
Unpacked	84	33	48	19	48	19	77	170
Crated *	92	36	61	24	102	40	110	200
Accessories and attachments								
Crated *	76	30	61	24	102	40	80	100

* For domestic shipment only.

As with any power-driven apparatus, the patients must be selected carefully. Without power the machine is not free-moving but requires more than minimal effort to start and maintain motion. Assistance to the pedal motion is possible by applying pressure on the handles, which are mechanically coupled to the pedals. The apparatus must be used with caution. This exerciser does not replace the foot-driven bicycles already in use. It is useful in rehabilitation of various parts of the body, including the arms, shoulders, back and lower extremities.

The Council on Physical Medicine and Rehabilitation voted to include the Brockman Therapeutic Exerciser in its list of accepted devices.

THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION
535 N. DEARBORN ST. - - - CHICAGO 10, ILL.

Edited by
AUSTIN SMITH, M.D.

Associate Editor
JOHNSON F. HAMMOND, M.D.

Editor for Current Medical Literature, GEORGE HALPERIN, M.D.

Subscription price - - Twelve dollars per annum in advance
Cable Address - - - - "Medic, Chicago"

SATURDAY, DECEMBER 16, 1950

THE CLEVELAND MEETING OF THE AMERICAN MEDICAL ASSOCIATION

The recent Clinical Session of the American Medical Association at Cleveland fulfilled once again the desires of those in attendance who were looking for up-to-date scientific information particularly intended for the general practitioner. It also indicated an increasing alertness on the part of the medical profession to its responsibilities in civic and other affairs that concern the health of the people of this nation.

Several thousand visitors, including physicians, medical students, nurses, exhibitors at the technical exhibits and guests, attended the meeting places for the Association's activities. The demonstrations and lectures sponsored in the Scientific Exhibit and lecture halls, the color telecast of surgical procedures and demonstrations, the medical motion pictures, the quality of the Technical Exhibit and the actions of the House of Delegates reflected clearly the breadth of activities and the interest of the participants at a Clinical Session of the American Medical Association.

SCIENTIFIC ACTIVITIES

The scientific sessions were planned to summarize current information on medical advances in various fields. Included in the general topics were discussions of cancer, heart and blood vessel diseases, diabetes, diseases of children, surgery, anesthesia and poliomyelitis. More than 80 prominent physicians participated in the lectures or demonstrations. Supplementing the lectures and demonstrations were 70 exhibits essentially devoted to the subjects mentioned. Even practical laboratory demonstrations were found as a prominent part of the scientific exhibits.

THE TECHNICAL EXHIBITS

More than 145 firms participated in the technical exhibits. Manufacturers of apparatus, dietary products and drugs and publishers were among those who were represented in this informative and interesting feature. During the past years there has been an obvious trend toward the development of more scientific presentations in the technical exhibits, and the commendations offered by passing physicians indicate the value of this trend.

HOUSE OF DELEGATES

The House of Delegates had a record attendance. Of 198 eligible delegates, 195 were seated on the opening day. They represent the constituent state and territorial associations, the Scientific Sections of the American Medical Association and the medical departments of the armed forces, the United States Public Health Service and the Veterans Administration. The large registration of delegates and their continued attendance revealed their serious interest in medical affairs. Perhaps most significant of the closeness of their interest is the fact that not one of the reports offered to the House by the Reference Committees was changed. As the Speaker of the House, Dr. F. F. Borzell of Philadelphia, pointed out, this surely indicated that the meetings of the Reference Committees had been well attended, the subjects thoroughly discussed and the delegates satisfied that the committees reported out the consensus of those in attendance.

The proceedings of the House of Delegates will be reported in THE JOURNAL beginning with the December 23 issue. Each action of the House will be given in sufficient detail to permit the reader to learn the reports of the reference committees and the disposition of these reports by the House. The complete proceedings will be made available as usual in a bound volume that will be sent to all officers of the Association and to all members of the House of Delegates. Others who may want a copy should communicate with Dr. George F. Lull, Secretary of the Association.

One of the earliest actions of the House was to choose the General Practitioner of the year, Dean Sherwood Luce of Massachusetts. Each county medical society is permitted to propose a candidate for this award. From these nominees one is selected from each state. The state list then is studied by the Board of Trustees, which presents three names to the House of Delegates, which by ballot selects the recipient.

The address of the President of the American Medical Association was published in the December 9 issue of THE JOURNAL. In the same issue appeared a statement from Mr. William L. Hutcheson, General President, United Brotherhood of Carpenters and Joiners of America, which was read before the joint meeting of the House of Delegates and the National Education Campaign. Because of illness Mr. Hutcheson could not appear, and his address was read by Peter E. Terzick, editor of *The Carpenter*. These addresses

and others of great interest and significance will be made available for the members of the profession through other mediums. Also available will be the addresses presented at the third annual Medical Public Relations Conference, which was held immediately preceding the meetings of the American Medical Association and which was attended by more than 300 persons interested in public relations.

SECTION ON MILITARY MEDICINE

The House of Delegates, following a recommendation from the Council on Scientific Assembly, established a new Section on Military Medicine.

MEMBERSHIP

In an early issue of THE JOURNAL will be another series of questions and answers relating to membership and fellowship in the American Medical Association. These will appear in the Organization Section of THE JOURNAL. In the meantime, because of the many questions that have been raised concerning them, a summary of some actions considered by the House of Delegates is reported here. The House decided that fellowship and membership dues should be continued. Annual dues for members will include subscription to THE JOURNAL of the American Medical Association, an action taken by the House of Delegates at the 1950 Annual Session. An active member will be considered delinquent if his dues are not paid by December 31 of the year for which dues are prescribed and shall forfeit his active membership in the American Medical Association if he fails to pay the delinquent dues within 30 days after the notice of his delinquency has been mailed by the Secretary of the American Medical Association to his last known address. The Board of Trustees may excuse a member from paying dues when it is deemed advisable, provided that the member is excused from payment of his full dues by his component society and constituent association. However, all physicians who are engaged in the active practice of medicine, regardless of whether they are excused from payment of dues by a state association, must pay dues to the American Medical Association unless such payment would be a hardship. A physician who pays only partial dues to his county and state societies owing to hardship will be exempted from payment of A. M. A. dues but will not receive THE JOURNAL. This exemption will not be granted, however, except on written recommendation of the secretary of the county or state society in which the physician resides.

COMMITTEE ON CONSTITUTION AND BY-LAWS

An Interim Committee on Constitution and By-Laws reported several recommendations to the House of Delegates. At the conclusion of the report the House adopted action whereby this committee will continue until the 1951 annual session of the House, at which time a permanent committee on the Constitution and By-Laws will be activated. The new standing committeee will consist of five member or service fellows elected by the House of Delegates on nomination by the Board of Trustees for terms of five years, so arranged that at each annual session the term of one member expires. The President, Secretary, Assistant Secretary, a member of the Board of Trustees and the Speaker and Vice Speaker of the House of Delegates will be ex officio members without the right to vote. The Committee will be fact finding and advisory and will report to the House of Delegates.

COMING A. M. A. MEETINGS

Among the items of general interest to the readers of THE JOURNAL is the supplementary report of the Council on Scientific Assembly which recorded the appointment by the Board of Trustees of Dr. James T. Billups of Houston, Texas, as Chairman of the Local Committee on Arrangements for the Houston Clinical Session to be held Dec. 4-7, 1951. The 1952 Clinical Session will be held in Denver during the first week in December and the 1953 Clinical Session in St. Louis.

BLOOD BANKS

In its consideration of the report of the Committee on Blood Banks, a Reference Committee of the House of Delegates recommended that the Board of Trustees urge that a state committee on blood banks be established in all constituent associations, that these committees be advised of the necessity of full cooperation with all other agencies engaged in blood procurement programs, that they promptly develop a blood program and that a copy of the report of the Committee on Blood Banks which appeared in the Handbook and the supplementary report presented to the House be sent to the secretary of each constituent association for the information of its blood bank committee.

A SUCCESSFUL MEETING

Those who attended the fourth Clinical Session of the American Medical Association left with a feeling that much was accomplished. This was made possible by the cooperation of all participants, and to them goes much credit for their hard work and interest in the development of this meeting. Particular credit, however, should be accorded the physicians in Cleveland who responded on such short notice when arrangements for this meeting in Denver had to be canceled because of local difficulties. The Local Committee on Arrangements worked unceasingly to make the meeting a success. The Chairman, Dr. Fay A. Le Fevre and the

members of the administrative and other committees that made the meeting possible deserve the warm praise given them by the House of Delegates as it closed its meeting.

GENERAL PRACTITIONER'S AWARD

At the recent annual clinical session in Cleveland, the House of Delegates of the American Medical Association awarded its Gold Medal "for exceptional service by a general practitioner" to Dr. Dean Sherwood Luce of Canton, Mass. His career is the prototype of that of thousands of general practitioners throughout the United States, who devote their lives to the care of the sick. The selection of a particular person for this honor, however, is carefully guarded by rules set up by the Association. Dr. Luce was born in Holliston, Mass., nearly 75 years ago, the son of a Yankee sea captain, who, after losing his ship and almost his life, opened a general store on Martha's Vineyard. Dr. Luce attended Phillips Andover Academy, and Harvard Medical School, returning to the island on week ends to look after the business. He graduated from Harvard and, after interning at the Long Island Hospital in New York, began to practice in Canton in 1905. He was still busy attending to his practice when notified of this award. For the formal presentation of the award before his fellow physicians, Dr. Luce flew to Cleveland. He has long been interested in medical organizational activities. He is a councilor of the Massachusetts Medical Society, a member of its Committee on Public Relations and a past president of the Norfolk District Medical Society and has been editor in chief of the official publication of that organization. Dr. Luce served as a captain in the Medical Corps of the Army in World War I and as a member of the Selective Service Board of his community in World War II. He has been a trustee of the Canton Public Library, a member of the Canton Board of Health, and the school physician of that city for more than 20 years. He is also a member of the senior staff of the Norwood Hospital in Norwood, which is in Norfolk County, as is Canton, his home town.

DEAN SHERWOOD LUCE, M.D.

NEW SUPPORT FOR MEDICAL EDUCATION

In an epoch-making statement, the Board of Trustees announced at the Cleveland meeting of the American Medical Association the appropriation of a half million dollars for 1951 as the nucleus of an annual fund to be raised for the aid of medical schools throughout the nation. This decision of the Board of Trustees was unanimously and enthusiastically adopted by the House of Delegates. The statement presented by Dr. Louis H. Bauer, Chairman of the Board, reads:

The Board of Trustees of the American Medical Association is pleased to announce to the House of Delegates that it has appropriated a half million dollars out of its National Education Campaign Fund, which was raised to defend medical freedom, for the aid and support of medical schools which are in need of additional financing. This fund will be given to the medical schools for their unrestricted use in their basic training of future physicians. This appropriation to aid the medical schools has been made possible by the widespread public cooperation which the profession has received from the American people in its campaign against compulsory health insurance. The fight against socialized medicine must go on until this issue has been clearly and finally resolved, but the pressure for regimentation of the medical profession has greatly lessened, owing to the magnificent public support which we have received. The Board of Trustees, therefore, feels that it is keeping faith with the American people, who have given medicine such a splendid vote of confidence, when it contributes this amount to the medical schools of the nation.

There is growing public awareness that federal subsidy has come to be a burden, not a bounty, for it is bringing intolerable increases in taxation and is dangerously increasing federal controls over our institutions and the lives of our people. American medicine feels very strongly that federal aid for medical schools should not be sought unless all other means of financing have been exhausted. The Board of Trustees announced yesterday its belief that funds for this purpose could be obtained from private sources—and as practical evidence of our sincerity of purpose, this appropriation has been made as the nucleus of a fund which we hope will be greatly augmented by contributions from many other sources.

The Board hopes that this action will become a stimulus to other professions, industries, businesses, labor groups and private donors to contribute to this very important cause of protecting and advancing the interests of medical education and the public health. The American Medical Association urges all its members to contribute individually to this cause, and we hope that doctors will take the lead in securing contributions from other sources.

Furthermore, the American Medical Association invites attention to the fact that it has been spending about a quarter of a million dollars a year for many years past to advance medical education through its Council on Medical Education and Hos-

pitals and other departments. This appropriation, voted today, for an entirely new purpose, is in addition to nearly $285,000 already budgeted for this work during 1951.

The nation's medical schools are of the greatest importance to every American citizen, and the American Medical Association has had the advancement of their standards as one of its main objectives for over 100 years. The Board of Trustees feels that, if all other organizations and individuals will render support of this worthy cause in accordance with their financial ability, not only will the financial security of medical schools be assured but their freedom will be protected.

Within hours after the Board's decision had been announced more than $6,600 was spontaneously pledged by individuals and several thousands from other sources. Details concerning the plan whereby others may give to the fund now are being worked out and will be announced in THE JOURNAL and through the *Secretary's Letter,* which is transmitted to all officers of the American Medical Association and of the state and county medical societies. Additional information may be obtained now from Dr. George F. Lull, Secretary of the Association, by those wishing to make an immediate contribution.

MILK-BORNE VIRUCIDE

Experimental evidence suggesting a milk-borne immunity against certain virus diseases was recently reported by Ratner,[1] Culbertson,[2] Curley [3] and others. Using murine poliomyelitis virus, Knox [4] of the Department of Bacteriology, Columbia University, confirms their evidence.

At various stages of gestation, 100 pregnant mice were inoculated orally with the murine virus. Eighteen viable litters were born to these inoculated mothers. Half the litter were reared by their own mothers, while others were reared by foster mothers, some of which were normal. Six additional litters were obtained from mothers not infected till after parturition, six litters from mothers of known immunity and four litters from normal mothers. Between the time of weaning and 44 days of age the young were tested for immunity by intranasal instillation of a 1:100 dilution of the murine virus. Older littermates and adults were tested by intraperitoneal inoculation with five times this dose. It was found that the immunity of the young was directly related to the immunity of the foster mother, rather than to the immunity of the natural mother. A nursing period of 10 days was sufficient to transfer complete protection against the test dose of murine virus.

Milk obtained from immune mothers was therefore pooled and tested for its in vitro capacity to neutralize murine poliomyelitis. While normal mouse milk had no detectable neutralizing power, milk from immune mice reduced the virulence of murine virus when tested in dilutions as high as 1:100 and completely neutralized the virus in a dilution of 1:10. The exact nature of the virucidal factor in immune mouse milk has not been determined.

1. Ratner, B.; Jackson, H. C., and Gruehl, H. L.: J. Immunol. **14**: 249, 1927.
2. Culbertson, J. T.: J. Immunol. **33**: 51, 1940.
3. Curley, F. J., and Gordon, J. E.: Am. J. Hyg. **48**: 81, 1948; J. Infect. Dis. **85**: 259, 1949. Anderson, J. A., and Bolin, V.: Am. J. Hyg. **50**: 200, 1949.
4. Knox, A. W.: Proc. Soc. Exper. Biol. & Med. **74**: 792 (Aug.) 1950.

REACTIONS TO DEXTROSE

Seibert [1] in 1923 demonstrated that the substance responsible for febrile reactions following administration of solutions by vein is a product of bacteria that exist in river water and in tap water. It is important to realize that it is not the bacteria that produce the reaction but their toxic products. Elimination of pyrogens, substances responsible for febrile reactions following administration of solutions by vein, is accomplished by a number of procedures, such as proper distillation and sterilization of glassware and tubing. Rademaker [2] stressed that the care of glassware and tubing constitutes the most important factor in elimination of such reactions. Some authors consider rapidity of infusion as being responsible for some of the shock symptoms of the postinfusion reaction.

However, according to Randolph and his co-workers [3] there remains a residue of reactions after all measures of control of pyrogens have been scrupulously adhered to and the speed of administration regulated. The fact that only a few patients have reactions, and that most do not, suggests that an individual idiosyncrasy or allergy plays a part. These authors stress that sensitivity to corn occurs as often as sensitivity to wheat, if not more so. It is therefore not surprising that there should be occasional reactions to intravenous injection of dextrose that is prepared from simple hydrolysis of cornstarch. These authors demonstrated that crystalline sugars prepared from cornstarch may cause intense allergic reactions when ingested by persons highly sensitive to corn. The rapidity of the onset and the severity of such clinical reactions suggest that the sugar is allergenic in the form administered rather than in some form occurring after ingestion. The specificity of these reactions is demonstrated by the fact that alpha-*d*-glucose prepared from beet sucrose fails to produce symptoms when ingested by the patient who is sensitive to corn and who reacts specifically to corn sucrose; conversely, glucose prepared from beet sucrose will produce allergic reactions when ingested by patients known to be sensitive to beets.

The authors were able to reproduce in five patients who showed great sensitivity on ingestion of corn and corn products similar allergic phenomena by intravenous injection of a 5 per cent dextrose solution. It therefore appears probable that some of the stormy postoperative courses may be explained on the basis of allergy to dextrose.

1. Seibert, F. B.: Fever Producing Substance Found in Some Distilled Waters, Am. J. Physiol. **67**: 90, 1923.
2. Rademaker, L.: Reactions to Intravenous Administration of Solutions, J. A. M. A. **135**: 1140 (Dec. 27) 1947.
3. Randolph, T. G.; Rollins, J. P., and Walter, C. K.: Allergic Reactions Following the Intravenous Injection of Corn Sugar (Dextrose), Arch. Surg. **61**: 554 (Sept.) 1950.

WASHINGTON NEWS

(From the Washington Office of the American Medical Association)

White House Conference on Children and Youth

In four crowded, hectic days in Washington, leaders in the nation's children and youth programs came to general agreement on what the young people need in health and other services. Their findings are embodied in the report of the White House Conference on Children and Youth, attended by 6,000 official delegates and observers.

"Children require, for their fullest development, full access to health, educational, recreational, social and religious services and programs directed toward the well-being of all they serve." This statement, taken from the preamble to recommendations, underlines all recommendations.

The final plenary session came to these conclusions regarding the health of young people: 1. More research is required on development and adjustment. 2. All states should establish standards for the hospital care of mothers and children, "in order to assure the quality of care that modern science knows how to give." 3. All-inclusive minimum standards for day-care center nursery schools and kindergardens should be established by state health or education departments. 4. Prompt action should be taken at the national level to provide funds to supplement those of states and localities "to stimulate the early development of adequate local (public) health services throughout the country, 'particularly in view of mobilization.' (A bill for federal aid to local public health units has passed the Senate but has been held up in a House committee. 5. In developing new housing facilities, special attention should be given to health, recreational and social needs, and children of migrant workers should be given the same benefits as all other children. One work section also came to the conclusion that "child health and welfare services are uneven in distribution and lacking in continuity and quality. Yet adequate services of this kind are basic for the development of healthy personality." Another section was even more critical: "Present health services have many inadequacies, particularly in relation to furthering healthy personality development in children and youth. Many now rendering such services do not fully understand or give attention to the dignity and emotions of the individual, which are necessary to healthy personality development. . . ." The same section also commented, ". . . success of . . . mobilization is to an important degree dependent on provision of adequate health services to our mothers, children and youth." Another section cited the need for adequate treatment programs for handicapped children, and a further expansion of health services for children in general.

In their final draft, recommendations omitted such controversial subjects as President Truman's national compulsory health insurance plan, aid to medical education and permanent and total disability insurance. However, these and almost every other subject in the health field were heatedly debated in work groups. A resolution endorsing compulsory health insurance came out of one work group, but did not reach the floor. Another called for permanent and total disability insurance as essential to the security of children, but this, too, was deleted before the resolution was presented for action by the plenary session.

Conference Notes

The 6,000 delegates to the conference made it one of the biggest meetings ever held in Washington; attendance was more than double that at the last White House Conference on Children and Youth. Invitations were issued to about 400 federal officials. Work groups were assigned topics that cut across professional lines, thereby insuring a variety of expression. With a two year build-up for the conference, demand for invitations was so great that a cutoff had to be imposed early in November. No specific "health" or "medical" topic was assigned, but reference to health and medical problems appeared in many of the recommendations. Delegates, all invited as individuals with particular interest in the problems of children, were selected mainly from three sources—national organizations working with children and youth, state organizations and youth participation organizations. This was the first time young people were asked to attend the Conference or participate in its planning. One hundred and eighty physicians attended; over 100,000 persons helped in preparations for meeting, 500 youth delegates participating. Subject matter of work groups ranged from infancy to young adulthood; from effects of the atomic bomb to cheating in school; from discrimination to television. . . . On Selective Service, Dr. William C. Menninger, Menninger Foundation, had this to say: "Selective Service always discriminates, as illustrated by the fact that psychological tests designed to eliminate 13 per cent are actually rejecting 24 per cent of those available for service." Referring to the current deferment of the top 50 per cent of college students, he said, "The men in service would then bear the stigma of low scholastic ability, and academic standards vary, so that the 'lower' group in one college would be considered 'upper' in others." . . . The 300 delegates attending a panel on effects of mass communications unanimously recommended that FCC allocate certain remaining television channels to educational institutions.

Stockpiling of Medical Equipment

American mayors, testifying on Civil Defense legislation before the Senate Armed Services Committee, urged that the federal government act promptly to start building up regional stockpiles of medical equipment. On this the mayors and civil defense officials are in agreement, and legislation appropriating $400,000,000 to buy medical and engineering supplies is before the committee. However, on two other important points the mayors are completely at odds with the federal program:

1. By unanimous vote, the American Municipal Association, made up of mayors, recommended that civil defense be made part of the Defense Department, but under civilian control. This is unlikely without a reversal of direction, in view of the fact that an independent Federal Civil Defense Administration was set up by President Truman on December 1 and already is functioning. The Senate committee has before it a bill (S. 4219) that would establish the administration by statute and give it unprecedented power to meet disaster problems.

2. In the same recommendation, the mayors urged that the federal civil defense organization establish and maintain direct ties with cities and communities, to assure them up-to-the-minute information and guidance in their preparations. In reply, James J. Wadsworth, deputy administrator of FCDA, pointed out that the whole civil defense program is based on delegation of responsibility, from federal to state and from state to local. He emphasized that federal civil defense authorities already have put out vast amounts of information in the form of pamphlets and booklets. Particularly, he requested the mayors to give the following information to citizens who ask "What can I do": "The Red Cross has mobilized its facilities and chapters to carry out three major activities in which everyone can take part. These are the first aid program, in which some 20,000,000 persons should be trained as rapidly as possible; the national blood program, in which the Red Cross will coordinate the efforts of all interested agencies in developing a realistic program of mass blood procurement, and the nurses aid and home nursing training, which will be carried out on a large scale."

The mayor's request for immediate action on medical stockpiles was presented to the committee by Mayor John B. Hynes of Boston, who also urged that medical equipment be standardized. Mayor Albert E. Cobo of Detroit supported this demand,

saying the cities had a right to know immediately what the federal government is going to do about stockpiling and standardizing medical as well as other supplies. Several other mayors voiced the same general opinions.

In earlier testimony before another Congressional committee, W. Stuart Symington, chairman of the National Security Resources Board, emphasized repeatedly that primary responsibility rested with states and communities. He said, "The greatest pressure of the operating load in civil defense rests squarely on the shoulders of our state and local governments. . . . The Civil Defense Office (at that time in N.S.R.B.) has pounded home constantly the theme that our states and cities must meet squarely the problems of heading up the grave and complex program which the international situation has imposed on every state and almost every city in our country. . . . (this) is the greatest challenge ever faced by our state and local governments. . . ."

Refilling of Prescriptions

Announcement of a proposed change in federal regulations on refilling of prescriptions has brought the whole subject again under discussion, this time with the probability of concrete developments. Federal Security Administrator Oscar Ewing has allowed 30 days for comments or protests to be filed, with the new regulations not to be put into effect until objections have been considered. The effect of the change, as now proposed, would be to allow pharmacists to refill prescriptions containing "over the counter drugs" without either written or oral prescription from the physicians. There would be no relaxation regarding so-called potent or prescription drugs, which still would have to carry the label "Caution: To be dispensed only by or on the prescription of a physician." FSA said, "We will continue to press legal action against those few pharmacists who endanger their customers' lives by selling these toxic drugs without prescription or on unauthorized refill." The complete text of the proposed regulation appears in the *Federal Register* for December 6.

Announcement that the change was contemplated came after the American Pharmaceutical Association had called for a public hearing on the whole issue of refilling prescriptions. Instead, FSA drew up the new regulations and allowed 30 days for comment or protests. As a consequence, objections from the Association or any other interested groups will be filed in writing rather than presented in open hearing. A spokesman for the American Pharmaceutical Association said that, if the regulations as finally drafted are not satisfactory, the association will go to court to enjoin FSA from putting them into effect.

Meanwhile, legislation to revise federal statutes on prescriptions appears to be definitely dead for this Congress. The Durham-Humphrey bill (H. R. 8904 and S. 3852) has two principal provisions: 1. Except for narcotics, "prescription legend" drugs could be filled on oral order from the physician, but he would be required to confirm the prescription in writing within 72 hours. 2. Clear definition would be made of drugs that would have to carry the prescription legend and "over-the-counter" drugs. Prescriptions for the latter could be refilled without reference to the physician. This bill has the support of the Food and Drug Administration, Federal Trade Commission and the retail druggists, but some of its provisions are opposed by the American Pharmaceutical Association.

Atomic Energy Commission Fellowships

The Atomic Energy Commission announces a total of 325 fellowships for the 1951-1952 academic year, divided as follows: 150 predoctoral in physical sciences; 100 in biologic sciences; 30 postdoctoral fellowships in physical sciences and 45 in biologic and medical sciences. The program will be administered by the Institute of Nuclear Studies, Inc., of Oak Ridge, with the National Research Council screening applicants. Final determination of fellows will be made by a national fellowship board to be appointed by the institute. Some type of security clearance is required for all fellowships. Predoctoral fellows receive $1,600 and postdoctoral $3,000, plus dependency allowances. AEC prefers to have postdoctoral fellowships served at an institution other than the one from which the fellow received his doctor's degree.

Chemicals in Foods

Recommendations for new legislation governing use of new chemicals in or on foods are almost certain to be made as a result of three months of intermittent hearings conducted by the House Select Committee on Chemicals in Foods. At this writing only one proposed bill is before the committee, that submitted by C. W. Crawford, Deputy Commissioner of foods and drugs, Food and Drug Administration, but committee members are expected to have some ideas of their own to submit to Congress. Mr. Crawford's bill would require producers of insecticides and other chemicals and preservatives for fresh and canned foods to submit their product to a specific series of tests before putting them on the market. Several witnesses have expressed the opinion that the residue from dusting and spraying compounds in some cases is dangerous to humans and that some other types of chemicals used in processing or packaging foods also are a hazard.

In the course of the hearings, Committee Counsel Vincent Kleinfeld complained that some representatives of the food industry have appeared reluctant to testify. The committee has not used its power of subpoena, but Mr. Kleinfeld said a few letters "requesting" attendance had been sent out when earlier invitations were ignored. Last week a group of agronomists, representing several universities and colleges, testified that chemical fertilizers if used properly are not harmful to man. Their argument was similar to that advanced earlier by a representative of producers of these agricultural chemicals, namely, that existing legislation is sufficient to protect the public and that, if there is any ground for concern, it is in the way the present laws are being enforced. Views of the food chemical industry (chemicals added to foods) were presented by Dr. John Foulgar of E. I. du Pont de Nemours & Co., supported by several other technical witnesses. He urged the committee to consider the disadvantages as well as the advantages of any new laws and stressed that many of these chemicals are important to the national diet. He advised the committee to make certain that any new test methods or standards required be reasonable and practical, as well as effective in protecting the health of the country. He said that, if the practical aspect of investigations were ignored, one result might be a slackening of efforts to develop new and improved ingredients. Dr. Foulgar suggested that the committee consider amendment of the Food, Drug and Cosmetic Act to require notice to Food and Drug Administration of intent to add to a food an ingredient not previously used in that food.

Notes

The full text of Executive Order 10186, establishing a Civil Defense Administration, appears in the *Federal Register* of December 5. The administration has less power under the executive order than under the proposed law. . . . "Sourcebook on Atomic Energy," the latest Atomic Energy Commission publication, is a 546 page book giving a review of basic nonsecret atomic energy information. . . . Bills to insure greatest possible distribution of N.S.R.B.'s pamphlet, "Survival Under Atomic Attack," are now before both House and Senate. N.S.R.B. has distributed over a quarter of a million copies. Copies may be purchased from the Superintendent of Documents, Government Printing Office, Washington 25, D. C., for 10 cents each. Incidentally, the latest word is that the health service manual for civil defense will be mailed to state Civil Defense directors before the first of the year. . . . The Senate subcommittee investigating health services has figures from commercial insurance companies, Blue Cross and Blue Shield. The committee is analyzing the statistics and has asked these groups for their opinions, which also will be analyzed for the report. . . . E. Roland Harriman has officially taken office as the new president of the American National Red Cross.

GOVERNMENT SERVICES

Army

Training Program Provided Physicians in the Emergency

At the beginning of the Korean conflict, only about 190 Army physicians were on duty in the entire Far East Command comprising Japan, Okinawa, Guam, the Philippines and Korea. As the troops in that area required a much larger number of physicians, the situation quickly became an emergency. Appeals were made to reserve officers, but of more than 3,000 who received letters, only 40 volunteered for immediate active duty. The Surgeon General's office considered next the young physicians who were serving in residency programs. The five large Army teaching hospitals already had small permanent and residency staffs, so that all residents could not be taken away from these hospitals. It was decided to reduce each service to the minimum necessary for the continuation of medical care in the hospital. This was done, and 132 residents, 101 young physicians who had just finished their internships and 89 civilian residents were flown to the Far East. The military stations throughout the United States were further depleted of medical officers, and they, too, were flown to the Far East, making in all, as of Nov. 7, 1950, about 750 medical officers in the Far East Command. The civilian residents were taken only after telegrams had been sent to the superintendents of the hospitals in which they were located requesting the release of these civilian residents as soon as possible. With few exceptions all agreed to assist. The value of the residency training program, which had been established after World War II, was indeed great in this emergency. The Army Medical Service was thus enabled to furnish medical officers promptly in all of the required specialties, and the medical care provided to the sick and wounded was creditable in every respect. In fact, according to Brig. Gen. Paul I. Robinson of the Surgeon General's office, in his address before the New England Post Graduate Assembly, Boston, Nov. 7, 1950, "There is every indication that an extraordinary record is in the making." General Robinson said that the wounded-in-action in the first three months of the Korean campaign equaled the number of American wounded in the first one and a half years of our participation in World War II. Nevertheless, the fatality rate for wounded soldiers reaching treatment centers, he said, will probably be less than half the World War II rate, which was 4.5 per cent.

Medical Draft Commission Deadline

In response to numerous inquiries relative to the final date on which draft eligible physicians may receive preinduction reserve commissions, Major Gen. Raymond W. Bliss, the Surgeon General, emphasized November 24 that the mechanics of processing applications preclude the guarantee of a commission to a registrant if he applies after receiving his induction notice. This commission deadline, General Bliss explained, is the result of administrative considerations. Section 5 of Public Law 779, 81st Congress, simply provides that "no person inducted under the provisions of this Act shall be entitled to the benefits of the provisions of Section 203 of Public Law 351, 81st Congress." However, for physicians and dentists to qualify as volunteers, and thus for the special professional pay authorized under Public Law 351, all processing required for a reserve commission must be accomplished and appointment made prior to induction.

"Because of the work load involved in processing an application for reserve commission, and the controls necessary for a decentralized Selective Service system, as well as a decentralized Army appointment system, we simply cannot guarantee that a registrant can receive his commission in time if he applies after he has received his induction notice," General Bliss said. "This, of course, does not preclude any registrant's applying for his commission after he has received his induction notice, and, if he receives a commission before actual induction, he is entitled to all the benefits provided for commissioned officers."

Personal

Col. Floyd L. Wergeland (MC) chief, Education and Training Division, Office of the Surgeon General, was honored by the College of Medical Evangelists, Loma Linda, Calif., on October 15, when he received the "Alumnus of the Year Award" at the annual alumni banquet in Los Angeles.

Navy

Admiral Boone Retires

Rear Admiral Joel T. Boone (MC), Inspector General, Medical Activities, retired on Dec. 1, 1950, with the rank of vice admiral after 36½ years of active duty in the Navy. In 1914 Admiral Boone entered the Navy as a lieutenant (junior grade). He served with the Marine Expeditionary Forces in Haiti and in 1916 participated in quelling the "Caco" (bandit) uprising, for which he received a Letter of Commendation from the Secretary of the Navy for "coolness under fire." In World War I, he served in France with the Second Army Division, participating in several major battles. For this service in France he was awarded the Medal of Honor by Congress for extraordinary heroism, conspicuous gallantry and intrepidity in conflict with the enemy.

During World War II Admiral Boone was Fleet Medical Officer. He was selected to be one of three officers to liberate Allied prisoners of war in Japan prior to the military occupation of that country and was the Naval Medical Corps representative at the surrender ceremonies of the Japanese aboard the *USS Missouri* on Sept. 2, 1945. He represented the Navy for three years as Director, Bureau of Naval Affairs, American Red Cross. In 1946 he was assigned as Medical Advisor to the Federal Coal Mines Administrator and as Director of the Medical Survey of the Coal Industry. In 1948-1949 he was Executive Secretary of the Secretary of Defense's Committee on Medical and Hospital Services of the Armed Forces. In 1949, Admiral Boone reported to the Secretary of Defense, having been appointed Chief of Joint Plans and Action Division, Office of Medical Services. During 1949 he served as president of the Association of Military Surgeons. Admiral Boone is the most decorated medical officer in the history of the Navy. He also had the honor of being physician to three Presidents, the late Presidents Warren G. Harding and Calvin Coolidge and later to President Herbert Hoover. Admiral and Mrs. Boone will reside in Washington for the immediate present at 4000 Cathedral Avenue, Northwest.

Personal

Rear Admiral Lamont Pugh, Deputy Surgeon General, has been elected president of the Washington Chapter of the University of Virginia Alumni Association.

Captains James R. McIntosh (MC, USNR), Bloomington, Ill., Clement C. Troensegaard (MC, USNR), Berkeley, Calif., and Lieut. (jg) Dwight M. Frost (MC, USNR) of Milwaukee, have been recalled to active duty at their own request.

Comdr. Harold A. Lyons (MC) has been appointed clinical assistant professor of medicine at the University of the State of New York College of Medicine.

Air Force

Dr. Boothby at Randolph Field

Dr. Walter M. Boothby, a professor emeritus of the Mayo Foundation, has joined the professional staff of the School of Aviation Medicine, Randolph Field, Texas, as research advisor. Dr. Boothby arrived at the school from Sweden, where for two years he had been advisor on research in aviation medicine and physiology to the Swedish Aviation Medicine Council at the University of Lund. While abroad he also appeared as guest lecturer at the universities of Aarhus, in Denmark, and Oxford and Cambridge, in England. At the Mayo Foundation Dr. Boothby was professor of experimental metabolism and, while there, organized the Mayo Aeromedical unit for research in aviation medicine. He is one of the original fellows of the Aero Medical Association, and is a fellow of the American College of Surgeons and of the American College of Physicians. During his long career Dr. Boothby has been instructor of anatomy at Harvard University Medical School, head of the Metabolism and Respiration Laboratories at Peter Bent Brigham Hospital, Boston, and chief of the Section on Metabolic Research at the Mayo Clinic. In World War I he was director of the First Corps Anti-Gas School and later instructor in the Army Medical School at Lange, France. He was at the front during the battles of St. Mihiel and the Argonne as chief of a surgical team. In 1938 he was a joint recipient of the Collier Trophy, in which he was cited by President Roosevelt for his contribution to aviation medicine in general and research on pilot fatigue in particular. He is a native of Boston and a graduate of Harvard University Medical School.

Gorgas Medal Presented to Major General Grow

At the annual dinner of the Association of Military Surgeons of the United States in New York, November 10, the Gorgas Medal was presented to Major Gen. Malcolm C. Grow (retired), former surgeon general of the U. S. Air Force. The medal and a $500 cash award was presented by Mr. H. W. Blades, executive vice president of Wyeth Incorporated, which pharmaceutical house established the medal in 1942 in honor of Surgeon General William Crawford Gorgas, whose work in preventive medicine made possible the construction of the Panama Canal. The recipient of the award is chosen annually by the Association of Military Surgeons.

According to the citation, General Grow "initiated, developed and made final arrangements for the employment of body armor to protect air force combat crews. He developed and put into use a device to protect gunners from wind blast; he developed electrically heated clothing, casualty bags for the wounded and wind and fire resistant face and neck protectors." General Grow was graduated from Jefferson Medical College in 1909. He retired on Nov. 30, 1949, after more than 31 years of military medical service.

Among the decorations and honors he holds are the Legion of Merit, Distinguished Service Medal, Bronze Star and French Legion of Honor in the rank of Chevalier, the Most Excellent Order of the British Empire, degree of Honorary Commander and the John Jeffrier Award. In 1949, General Grow was certified by the American Board of Preventive Medicine and Public Health.

Medical Supplies Dropped by Parachute

The 307th Airborne Medical Battalion, 82 Airborne Division, on October 26, pioneered the first heavy drop by parachute of major medical equipment. With no precedent to guide them, the 307th in conjunction with the Airborne Section of Army Field Forces Test Board no. 1, loaded a complete surgical operating unit on a heavy drop skid and dropped it from the rear of a C-82 aircraft. Another skid consisting of two complete hospital ward tents was also loaded and dropped. The first load landed without damaging a single item of equipment, which included such fragile items as thermometers, test tubes, a microscope and many delicate surgical instruments. The equipment, most of which had never been dropped by parachute before, included such items as a four section hospital tent, an autoclave (steam sterilizer) weighing 350 pounds, a complete field laboratory, two operating room lamps with batteries and a small generator, litters, blankets, surgical gowns and all the drugs needed for an extended stay in the field. The entire load weighed 4,500 pounds net. The second skid consisting of two hospital ward tents, with equipment necessary to care for all types of patients landed without mishap.

Veterans Administration

Benefits Authorized for World War II Veterans

The "Fact Sheet" released by the Veterans Administration Nov. 15, 1950, points out that the following medical and domiciliary benefits are authorized for World War II veterans:

Hospitalization.—World War II veterans, if discharged or separated under conditions other than dishonorable, are entitled to VA hospital treatment, under the following priority system: first, emergency cases; second, those suffering from injuries or diseases incurred or aggravated in line of duty during wartime service and third, those who state under oath that they are unable to pay hospital charges for treatment of non-service-connected disabilities or illnesses. These veterans, if not in the emergency category, must wait until a bed becomes available.

Emergency patients may be taken directly to the nearest VA hospital. If possible, the veteran, or someone acting for him or her, should communicate with VA by telephone or telegraph. In all other cases, the veteran, or his nearest relative, guardian or representative, should fill in the proper form for hospital care. These forms are available at any VA office.

If admission to a VA hospital or home has been approved, government transportation may be provided as follows:

1. Hospitals: To the hospital and, on completion of treatment in service-connected cases, to his or her home. This service may be provided for non-service-connected cases if they are unable to pay for the transportation.
2. Homes: To a VA domiciliary home.

Domiciliary care is designed to provide a "home" for veterans who have a chronic condition that incapacitates them from earning a living and who require minimal medical attention. Requirements for admission for domiciliary care are essentially the same as for hospital treatment. Transportation at government expense as a rule is provided only for the initial admission. The veteran, or his nearest relative, guardian or representative, should obtain preadmission approval from the nearest VA installation having facilities for domiciliary care.

Outpatient medical care is available for veterans in need of treatment for service-connected disabilities. Under this plan, eligible World War II veterans may receive treatment at VA hospitals or other field stations furnishing medical treatment or from approved private physicians. Each veteran's eligibility must be determined by VA before treatment of this type can be authorized. Necessary drugs may be obtained from "home town" druggists at government expense by veterans who are authorized to report to private physicians for treatment.

Personal

Dr. Franklin G. Ebaugh, professor of psychiatry, University of Colorado, conducted a two day seminar on the treatment of emotional disorders at the Veterans Administration Hospital, American Lake, Wash., October 2-3.

Dr. Knut Lindblom, Stockholm, Sweden, addressed the staff of the Crile Veterans Administration Hospital, Cleveland, October 2, 1950 on "Arthrography of the Knee" and "Myelography and Disk Puncture."

Dr. John J. Tyson has been appointed manager of the VA hospital in Omaha, which is scheduled to admit its first patients in November.

MEDICAL NEWS

(Physicians will confer a favor by sending for this department items of news of general interest: such as relate to society activities, new hospitals, education and public health. Programs should be received at least two weeks before the date of meeting.)

ALABAMA

Tenth Anniversary of Poliomyelitis Center.—A conference commemorating the tenth anniversary of Tuskegee Institute's treatment and training center for infantile paralysis was held November 27-28 in Tuskegee. Basil O'Connor, New York, president, National Foundation for Infantile Paralysis, was among the speakers who addressed 300 delegates and volunteer workers representing the foundation's chapters in various states. The celebration also served as a precampaign conference for the 1951 March of Dimes. Tuskegee's infantile paralysis center for Negro poliomyelitis patients and medical workers was established through a grant from the foundation. It is a three story brick building, a separate wing of the John A. Andrew Memorial Hospital, with which its work is coordinated.

CALIFORNIA

Short Poliomyelitis Courses.—Orthopaedic Hospital, Los Angeles, will give three short courses in poliomyelitis for physicians during 1951, aided by a grant from the National Foundation for Infantile Paralysis. Covering all phases of patient care, the courses will emphasize teamwork by professional services. New apparatus and methods for acute poliomyelitis treatment will be presented through cooperation with the Los Angeles General Hospital. Classes are scheduled for February 12-15, May 21-24 and October 22-25. Information may be obtained and enrolment made through C. L. Lowman, M.D., 2400 S. Flower Street, Los Angeles 7.

Voters Approve Release of Animals for Research.—The voters of Los Angeles on November 7 approved a proposition releasing an estimated 50,000 unwanted unclaimed dogs and cats from city pounds to qualified research institutions that are certified by the city health officer and inspected by the Department of Animal Regulation. A citizens committee conducted a campaign jointly with the Medical Research Society of Southern California, while the San Francisco County Medical Society contributed financially. Among the defense projects which have been hampered by a lack of animals for research is an Atomic Energy Commission program at the University of California School of Medicine, Los Angeles, to develop protective treatment against radiation effects of atomic bombs. A vital Navy aviation program to improve safety of high altitude jet flight was slowed down. Individual physicians also contributed to the successful campaign by urging their patients to vote for "Proposition C." Posters were placed in waiting rooms and drug stores. A tabloid newspaper captioned "Citizens Committee News for Yes on Proposition C" was widely distributed.

COLORADO

University Appointment.—Dr. John A. Frank has been appointed assistant professor of psychiatry in the University of Colorado department of medicine and a senior staff physician at the Colorado Psychopathic Hospital, Denver. One of his duties is to take charge of the 1927 Colorado law cases, that is, the examination of criminals who are making pleas of insanity. Dr. Frank comes to the university from Bellevue Hospital in New York, where he did similar work. He has been on the faculty of New York University since 1944.

CONNECTICUT

Personal.—Dr. Samuel C. Harvey, New Haven, has been appointed state director for the selection of physicians under the recently enacted Doctor-Draft Act. Serving with Dr. Harvey will be Dr. Stanley H. Osborn, state commissioner of health, and William R. Dunleavy, New Haven, dental advisor.

Dr. Murdock Honored.—Dr. Thomas P. Murdock, Meriden, member of the American Medical Association's Board of Trustees, was guest of honor at a testimonial dinner in New Haven November 29, in recognition of his many years of service to the medical profession. The event was held at the New Haven Country Club. Among the speakers were Dr. Louis H. Bauer, New York, Chairman of the American Medical Association's Board of Trustees; Dr. Edward R. Cunniffe, chairman, Judicial Council of the Association; Dr. Hart E. Van Riper, New York; Dr. Morris Fishbein, Chicago, and Dr. Creighton Barker, executive secretary, Connecticut State Medical Society. Dr. Thomas J. Danaher, Torrington, president of the state medical society, presided. Dr. Murdock is a past president of the state medical society and the New Haven County Medical Association. For several years he has been a member of the House of Delegates of the American Medical Association. In 1949 he was chairman of the A. M. A. Committee to Survey Nursing Services in the United States. He was a member of the Connecticut Medical Examining Board for 15 years.

ILLINOIS

Narcotic Violation.—Dr. John W. Long of Robinson recently pleaded nolo contendere at Danville to an indictment charging violation of the federal narcotic law and on September 11 was fined $500.

Chicago

Personal.—Col. Arnold D. Tuttle (MC, USA, retired), now medical director for United Air Lines, gave the graduation address for the aviation medical examiner class, School of Aviation Medicine, Randolph Field, Texas, December 2. Colonel Tuttle is a former commandant of the School of Aviation Medicine.

Society News.—The Chicago Society of Physical Medicine and Rehabilitation will meet January 24 at 8:00 p. m. in the Medical Center, Y. M. C. A., 1804 West Congress Street. Arthur H. Steinhaus, Ph.D., professor of physiology, George Williams College, Chicago, will speak on "Physiology of Exercise." Professional personnel and their guests are welcome.

Committee to Select New Department Head.—Dr. Warren H. Cole has been appointed chairman of a committee that will select a new head for the department of medicine at the University of Illinois College of Medicine and the university's Research and Educational Hospitals. Dr. Robert W. Keeton, present head of the department of medicine, will reach the retirement age of 68 during the present academic year. On the committee with Dr. Cole are Drs. Granville A. Bennett, George M. Hass, Francis J. Gerty, Henry G. Poncher, Francis E. Senear and George E. Wakerlin.

Chicago Medical School Appointments.—Dr. Herman Josephy, attending neuropathologist at the Chicago State Hospital, has been appointed associate professor of neurology at the Chicago Medical School. From 1914 until 1933 when he left his native Germany, Dr. Josephy was a physician at the Psychiatric Hospital in Hamburg, and from 1924 to 1933 he was an associate professor of neurology at the University of Hamburg. Harold Elishewitz, Ph.D., has been appointed assistant professor of parasitolog in the department of microbiology and public health. He emered the research and development branch of the Quartermaster General, Research and Development, U. S. War Department, in Washington, D. C, in 1943 and served also as recording secretary of the National Research Council Committee on Insecticides and Insect Repellents. The following two years he was associated with the Pan American Sanitary Bureau in South America and Southern Mexico.

New Program for Nurses at Northwestern.—Northwestern University Medical School has announced a new program for nurses that offers a Bachelor of Science degree in nursing in addition to the diploma in nursing. Candidates for the degree must have 90 quarter hours in an accredited university and must complete three calendar years in one of the schools of nursing affiliated with Northwestern University. These are Wesley Memorial Hospital and Passavant Memorial Hospital, both located on the Chicago Campus, and Evanston Hospital. Under the new program residence in Northwestern's College of Liberal Arts is not required. Credit from any accredited university will be accepted, but work in English, chemistry and biology is required. The new program, formulated by the Council on Nursing Education, was requested by the Northwestern Senate last June. Dr. John H. Annegers Jr., assistant

professor of physiology, is the coordinator and director of the program in nursing, under Dr. Van Dellen, director of the newly created Division of Auxiliary Medical Services.

INDIANA

Physicians in General Assembly.—When the 87th Indiana General Assembly opens, on January 4, three physicians will be among its members: Dr. William M. Cockrum of Evansville, a delegate from Indiana to the American Medical Association House of Delegates, and Dr. Otis A. Koop of Anderson, who were elected to the House of Representatives last month, and Dr. Walter F. Kelly of Indianapolis, a holdover senator.

IOWA

Fellowships in Basic Sciences.—Two fellowships supported by the Medical Service Funds of the State University of Iowa College of Medicine are being offered to graduates in medicine who contemplate academic careers. These are offered on the basis of half-time teaching and half-time research in any of the following departments: anatomy, bacteriology, biochemistry, pathology, pharmacology, physiology and hygiene and public health. Candidates may or may not have had clinical internships. Clinical residency trainees are acceptable if they wish to complement or interrupt a clinical residency program. Graduates of any approved medical school may apply. The salary will be $3,600 on a 12 month basis for those who are unmarried and $4,000 per year for those who are married. Application blanks may be obtained from the Office of the Dean, College of Medicine, State University of Iowa, Iowa City. Applications should be submitted to the same address on or before April 1, 1951.

KENTUCKY

Mobile Water Laboratory.—The State Health Department has a new $12,000 laboratory trailer fully equipped to take pollution tests along the Ohio River as part of a six state survey.

Cancer Society.—At the annual achievement dinner of the Kentucky Division of the American Cancer Society in Louisville November 14, Kenneth C. D. Hickman, Ph.D., of the Eastman Kodak Company, Rochester, N. Y., spoke on "Time and the Cancer Problem." The dinner honoring the 120 volunteer county organizations was attended by 250 workers throughout the state.

Personals.—At a meeting of the State Medical Research Commission November 16, Dr. Carl C. Howard, Glasgow, was reelected chairman, a position which he has held since the group was organized in 1948.——Dr. Harold M. Kelso, Louisville, has resigned as director of county health work of the State Department of Health, effective January 1. He will assume his former position of assistant city health officer, Knoxville, Tenn.

MASSACHUSETTS

Putnam Fellowship Open.—The Helen Putnam Fellowship for advanced research in genetics or mental health, open to women scholars who have a doctorate, is being offered by Radcliffe College for the academic year 1951-1952. The award carries a stipend of $2,800 a year with the possibility of renewal. Applicants are asked to submit a plan of research. Preference will be given those whose research is already in progress. Applications should be returned to the Secretary of the Graduate School, Radcliffe College, Cambridge, not later than April 1, 1951.

MICHIGAN

Pilot Blood-Typing Program.—Nurses, medical technologists and clerks began the first week of this month a project to type blood of students and faculty members at Wayne University, Detroit. The program, tentatively scheduled to run until the Christmas holidays, is part of a larger project being conducted by the state Office of Civilian Defense. The program is a "pilot study to see what problems are involved in a cooperative study of this kind." A uniform method of typing has been adopted by the whole state. Michigan cities taking part in the project are Jackson, Birmingham and Ypsilanti.

MISSOURI

General Practitioners Study Club.—The following programs for 1951 featuring local physicians have been arranged by the General Practitioners Study Club of Greater St. Louis:

Jan. 17, Norman Tobias, Office Treatment of Common Skin Diseases.
Feb. 21, Robert W. Bartlett, Differential Diagnosis and Treatment of Pain in the Right Upper Abdominal Quadrant.
March 21, W. G. Klingberg, Genitourinary Conditions in Childhood.
April 18, Robert E. Bruner, Early Diagnosis and Treatment in Cerebral Palsy.

NEVADA

Society Election.—The Nevada State Medical Association at its convention in October installed Dr. Walter F. Quinn of Ruth as president. Dr. J. Vernon Cantlon, Reno, was chosen president-elect; Dr. Leslie A. Moren, Elko, first vice president, and Dr. Clare W. Woodbury, Las Vegas, second vice president. The next annual meeting of the association will be held in Reno in October 1951.

NEW YORK

Postgraduate Instruction.—The Medical Society of the State of New York with the cooperation of the New York State Department of Health has arranged two lectures for the Jefferson County Medical Society, meeting in the Black River Valley Club, Watertown, at 6:30 p. m.

Dec. 19, Robert B. Burtch, Alexandria Bay, N. Y., and D. Naldrett White, Kingston, Canada, Recent Viral Disease Epidemic at Alexandria Bay.
Jan. 18, Nathaniel Kwit, New York, Management of Congestive Failure.

Dr. Small to Head Psychiatry Department.—Dr. S. Mouchly Small, New York, has been appointed head of the department of psychiatry at the University of Buffalo School of Medicine. He will also be director of psychiatry at Meyer Memorial Hospital. Dr. Small has been assistant resident in psychiatry at the Institute of Human Relations in New Haven, Conn., assistant resident and resident psychiatrist at the Payne Whitney Psychiatric Clinic of New York Hospital, instructor in psychiatry at Cornell and assistant medical director and consultant in psychiatry, National Hospital for Speech Disorders, New York. From 1943 to 1947 he was consultant in psychiatry to the American Cyanamid Corp., serving simultaneously as consultant in psychiatry and neurology at Vassar College. He was a psychiatrist at New York Hospital Rehabilitation Clinic from 1944 to 1946. Since 1947 Dr. Small has been neuropsychiatric consultant to the Surgeon General of the U. S. Army, serving also as consultant and lecturer to the Veterans Administration and lecturer at Columbia University College of Physicians and Surgeons.

New York City

Fourth Harvey Lecture.—Alfred E. Mirsky, Ph.D., member of the Rockefeller Institute for Medical Research, will deliver the Fourth Harvey Lecture of the current series at the New York Academy of Medicine on December 21, on "Chemical Aspects of the Cell Nucleus."

Personals.—Dr. Emil Froeschels has been made head of the new clinic for speech and voice disturbances at Beth David Hospital.——Dr. James W. Smith, assistant clinical professor of ophthalmology, has been promoted to clinical professor of ophthalmology at the Post Graduate Medical School of the New York University of Bellevue Medical Center.

Cancer Memorial Fund Check for Research.—A check for $100,000, from funds collected for the Damon Runyon Memorial Fund, was presented to the Sloan-Kettering Institute for Cancer Research at a luncheon November 10. The check was given to Dr. Cornelius P. Rhoads, director of the Memorial Center for Cancer and Allied Diseases, with which the institute is affiliated.

Friday Afternoon Lectures.—The twenty-fourth series of Friday Afternoon Lectures being given by the New York Academy of Medicine at 4:30 p. m. is open to physicians and to medical students. Lectures through February in the series are as follows:

Dec. 15, Oskar Diethelm, New York, Advances in Treatment of Chronic Alcoholism.
Jan. 5, J. Lester Gabrilove, New York, Virilizing Syndrome in Man.
Jan. 12, Sydney Farber, Boston, Newer Agents in the Treatment of Acute Leukemia.
Jan. 9, André Cournand, New York, Newer Methods in Diagnosis of Congenital Cardiac Anomalies.
Jan. 26, Judah L. Ebin, New York, Surgical Treatment of Parkinsonism, Indications and Results.
Feb. 2, William J. Grace, New York, Experimental Study of Chronic Ulcerative Colitis.
Feb. 9, Robert S. Hotchkiss, New York, Diagnosis of Testicular Deficiency States.
Feb. 16, Arthur H. Blakemore, New York, Shunt Operations for Treatment of Portal Hypertension with Special Reference to Cirrhosis of the Liver.

Pay Blue Cross Subscription with Rent.—With the enrolment of 252 residents of Bell Park Gardens, veteran's cooperative housing project in Queens, New York's Blue Cross Plan established a precedent by arranging for subscription fees to be paid along with the rent. The veterans and their family dependents were eligible for enrolment beginning December 1. It is reported that at least an equal number of families living in Bell Park Gardens are already receiving Blue Cross

coverage through groups in organizations where they are employed. Associated Hospital Service, New York's Blue Cross Plan, is a nonprofit, hospital-sponsored organization, which now serves 4,500,000 persons in the Greater New York area.

Admissions Committee Reorganized.—The Office of Admissions of the New York University College of Medicine has been reorganized. Dr. H. Sherwood Lawrence has been appointed secretary of the Committee on Admissions. In order to allow the most thorough consideration of the qualifications of candidates seeking admission, enlargement of the college's Office of Admissions became necessary because of the problems arising from multiple applications for entry into medical schools. More than 2,500 applications had been made for the 125 places in the college's first year class. Almost every candidate applied to several schools, Dean Currier McEwen said, while some were known to have applied to as many as 40 schools at once. Dr. Lawrence is an instructor in medicine.

TEXAS

A. O. A. Chapter at Southwestern.—At the installation dinner of the Alpha Omega Alpha honorary medical society chapter at Southwestern Medical College, Dallas, November 10, Chauncey D. Leake, Ph.D., Galveston, spoke on "The History of Medical Ethics." Dr. Walter L. Bierring, Des Moines, Ia., president of the fraternity, and Dr. Josiah J. Moore, Chicago, secretary, were the installing officers. President T. S. Painter of the University of Texas was made an honorary member and presided at the dinner.

Postgraduate Medical Assembly.—The International Post-Graduate Medical Assembly of Southwest Texas will be held in San Antonio at the Municipal Auditorium January 23-25, under the presidency of Dr. Merton M. Minter, San Antonio. Among the speakers will be:

Frank L. Meleney, New York, Intelligent Use of Antibacterial Agents.
Keith J. R. Wightman, Toronto, Canada, Clinical Disturbances of Fat Absorption.
C. Wilbur Rucker, Rochester, Minn., Lesions at the Optic Chiasm.
Hugh F. Hare, Boston, Effect of Radiation on Personnel.
Isador S. Ravdin, Philadelphia, Gallstone Disease.
Oscar Swineford Jr., Charlottesville, Va., ACTH and Cortisone in Allergic Diseases.
Mather Clevelana, New York, Intracapsular Fractures of the Neck of the Femur.
Alexander A. Weech, Cincinnati, Certain Aspects of Infant Feeding.
M. Ruiz Castaneda, México, D. F., Problems Concerning Epidemiology, Pathology and Pathogenesis of Brucellosis.
James H. Wall, White Plains, Psychoneurotic Conditions with Particular Emphasis on Obsessive and Compulsive States.
Walter B. Hoover, Boston, Dizziness from the Otolaryngological Standpoint.
William W. Scott, Baltimore, Geriatrics with Special Reference to Urological Problems.
Charles H. Slocumb, Rochester, Minn., Conditions in Which ACTH and Cortisone Are of Value.
Frank R. Lock, Winston-Salem, N. C., Management of Prolonged Labor.
William A. Meissner, Boston, Pathologic Observations on Thoracoplasty Failure in Tuberculosis.

The fee of $20 should be sent to International Post-Graduate Medical Assembly, P. O. Box 2445, San Antonio, Texas.

VIRGINIA

Narcotic Violations.—Dr. Ernest B. Nuckols, Cumberland, pleaded guilty to an indictment charging violation of the federal narcotic laws in the U. S. District Court at Lynchburg. On June 5 his sentence of one year and one day was suspended and he was placed on probation for a period of three years. He was also fined $10,000, which was to be paid within 60 days.

Dr. Marshall T. Garrett of Charlottesville pleaded guilty to an indictment charging violation of the federal narcotics laws in the U. S. District Court at Lynchburg. On June 5 his sentence of one year and one day was suspended and he was placed on probation for a period of three years. He was fined a sum of $2,500, which was to be paid within 60 days.

WISCONSIN

Marquette University Appointments.—Dr. William W. Engstrom, who has been associated with the Yale University School of Medicine since 1946, was one of three assistant professors named this fall to the staff of Marquette University School of Medicine, Milwaukee. Others appointed are Dr. John E. Steinhaus, department of pharmacology, and Dr. B. Wesley Catlin, former associate in research at Carnegie Institute, Long Island, N. Y. Dr. Michael W. Shutkin, attending physician at Mount Sinai Hospital, Milwaukee, has been made an assistant clinical professor of medicine. Four Milwaukee physicians have joined the Marquette staff as clinical instructors. They are Drs. Paul S. Pierson, Lloyd F. Jenk, Walton D. Thomas and E. Franklin Carl. Two Marquette medical faculty members were recently promoted to the rank of full clinical professors. They are Drs. Edward R. Krumbiegel, Milwaukee city health commissioner, Marquette Department of Public Health, and Gerhard D. Straus, department of otolaryngology.

GENERAL

Dr. Myers Named Dearholt Medalist.—Dr. J. Arthur Myers, Minneapolis, was named the recipient of the 1950 Dearholt Medal, given annually by the Mississippi Valley Conference on Tuberculosis for outstanding contributions to tuberculosis control. Dr. Myers is a past president of the National Tuberculosis Association, chief of the University of Minnesota Chest Clinic and a former member of the editorial board of the *American Review of Tuberculosis*, publication of the American Trudeau Society. He has written a history of antituberculosis work in Minnesota.

Plague Infection in Fleas.—According to the U. S. Public Health Service, in a report dated October 20, plague infection was proved positive in 17 fleas taken from two wood rats trapped April 22 about 17 miles east of Albuquerque in Bernalillo County, New Mexico. Under the same date the service reported that plague infection was proved positive in the following specimens taken two and a half miles west of Perico in Dallam County, Texas: 118 fleas from one prairie dog shot October 10 and 118 fleas flagged October 7 from prairie dog burrows.

Treatment Centers for Emotionally Disturbed Children.—A national survey of treatment centers that handle emotionally disturbed children will be made by the Child Welfare League of America under a grant of $26,000 from the Marshall Field Foundation. The purpose of the study is to analyze the best means of aiding emotionally disturbed children and preventing juvenile delinquency. The league will also provide consultation service to communties, social agencies and individuals interested in this work. Joseph Reid, assistant director of the league, will direct the survey.

Fraternity Fellowship Awarded.—Kappa Kappa Gamma, women's college fraternity, has awarded the $2,000 Harriet Ford Griswold Fellowship for study of rehabilitation in physical medicine to Dr. Yaeko Kawai, of Tokyo. The grant will provide transportation, lodging, food and incidental expense. New York University-Bellevue Medical Center, department of physical medicine and rehabilitation, will provide free tuition. The International Society for the Welfare of Cripples will administer the grant. Dr. Kawai was valedictorian of her class at Women's Medical College in Tokyo and since graduation has been engaged in research work at the biochemical laboratory of Nihon University.

Dr. Cook Honored.—Resolutions passed at the recent decennial meeting of the U. S. Pharmacopeial Convention were presented to E. Fullerton Cook, Pharm. D., Philadelphia, retired U. S. P. Revision chairman, at a luncheon on November 28. The luncheon was attended by most of the members of the board which served during the 1940-1950 decade as well as many of the present board. Dr. Cook was associated with the Pharmacopeia for 50 years. He served as assistant to the chairman of the U. S. P. Committee of Revision for almost 20 years and held the chairmanship from 1920 to 1950. His leadership helped make possible great contributions to the advancement of pharmacy, medicine, dentistry and other related sciences. The resolutions of the convention were presented to Dr. Cook in the form of an embossed and illuminated framed scroll.

Student Nurse Admissions Reach Five Year Record.—Schools of nursing throughout the United States admitted in 1950 the largest class in five years, according to the Committee on Careers in Nursing. A total of 44,185 first year students were admitted to the nearly 1,200 state-approved schools offering basic nursing programs, representing an increase of 1.3 per cent over admissions for the preceding year. The largest percentage increases were reported by Mississippi and Louisiana, 28 and 53 per cent, respectively. Although total admissions were up, 26 states showed fewer students admitted than in 1949, seventeen of these in the southern and far western sections of the country. Decreases of as much as or more than 15 per cent were reported in the District of Columbia, South Carolina, Montana, Arkansas and Arizona.

Society Elections.—At the annual meeting of the American Society for the Study of Arteriosclerosis in Chicago in November Dr. E. Cowles Andrus, Baltimore, was installed as president, and Dr. G. Lyman Duff, Montreal, was chosen vice president. Dr. Otakar J. Pollak, Quincy, Mass., was reelected secretary-treasurer.——At the recent meeting of the American Chemical Society Richard O. Roblin Jr., Ph.D., Stamford, Conn., was elected 1951 chairman of the Division of Medicinal Chemistry. Chester M. Suter, Ph.D., Rensselaer, N. Y., was elected vice

chairman and Marcus G. Van Campen, Ph.D., Cincinnati, secretary-treasurer.——The Central Society for Clinical Research has elected the following officers to serve in 1951: Dr. William B. Bean, Iowa City, president; Dr. William B. Wood Jr., St. Louis, vice president, and Dr. Kenneth G. Kohlstaedt, Indianapolis, secretary-treasurer.

Surgeons Sectional Meetings.—The first of a series of seven sectional meetings of the American College of Surgeons will be held in St. Louis on January 22-23, with headquarters at the Hotel Statler. The other sectional meetings will be held in Hot Springs, Va., February 26-27; Philadelphia, March 5-6; New Haven, Conn., March 16-17; Portland, Ore., March 26-27; Denver, April 6-7, and Detroit, May 10-11. The medical profession at large and medical students are invited to the meetings. The St. Louis meeting, opening at 8:30 a. m. both mornings with medical motion pictures, will be followed at 10:00 a. m. by a scientific session on Surgery for Ischemic Diseases, Emergency Management of the Injured Chest, Fractures about the Ankle Joint, and Hematuria Following Trauma: Present Means of Diagnosis and Treatment. At a dinner the first evening Dr. Melvin A. Casberg, dean, St. Louis University School of Medicine, will speak on "The Medical Organization of the Chinese Communists." From 8:30 to 10:00 p. m. there will be a symposium on cancer. On the day following the sectional meeting in St. Louis, January 24, a full day of clinics will be held in St. Louis hospitals for the visiting surgeons.

WHO Sets Standards for 16 Biological Substances.—An international standard for pituitary adrenocorticotropic hormone (ACTH) has been established by the Expert Committee of the World Health Organization on Biological Standardization. Meeting in Geneva in November, the committee also set up international standards for 15 other biologic substances, including certain vitamins, hormones, antibiotics, serums and antitoxins. (Thirty-nine biologic preparations had already been standardized either by WHO or, previously, the Health Organization of the League of Nations.) International biologic standards are provided by WHO in order to enable research workers and manufacturers everywhere to have a single, internationally accepted measure for the activity of the substances which they produce. Among some of the most important standards established last week, were also those for anti-Rh, and anti-A and anti-B blood-grouping serums: lecithin and cardiolipin, tubocurarin, streptomycin and dihydrostreptomycin, aureomycin, terramycin and diphtheria toxoid. A standard was also set up for hyaluronidase. In addition, in order to facilitate research on antibiotics, the committee decided to recommend the establishment of an international collection of specimens of new antibiotics to be made available to scientists all over the world. The international collection of new antibiotics recommended by the Expert Committee would consist of preparations contributed by research workers and found to present clinical and research interest. It would be kept at the National Institute for Medical Research (London) for distribution on request to scientists anywhere in the world. The committee also reported progress in standardizing vaccines. Examination of samples suitable to serve as standards is being carried out on cholera, whooping cough and smallpox vaccines in various laboratories.

Courses in Use of Radioisotopes.—The eighteenth, nineteenth and twentieth courses in the technics of using radioisotopes in research will be given by the Special Training Division of the Oak Ridge Institute of Nuclear Studies during the winter and spring of 1951. Dates for the courses are January 8-February 2, February 19-March 16 and April 16-May 11. The courses consists of laboratory work, lectures on laboratory experiments, general background lectures and seminars on special topics. Experiments are conducted covering the use and calibration of instruments, the purification and separation of radioactive materials from inert and other radioactive materials, measurement and use of C^{14}, pile activations, radioautographs and the like. Seminars include the use of radioisotopes in animal experimentation, use of radioisotopes in humans, principles and practice of health physics, design of radiochemical laboratories and effect of radiation on cells. The Special Training Division can accommodate 32 participants at each of the three courses. A registration fee of $25 is charged, and participants will bear their own living and traveling expenses. A two week advanced course in radioisotopes will be given by the Oak Ridge Institute of Nuclear Studies beginning February 5. The course is intended for research workers in the field of medicine who have had experience in the basic technic of using radioisotopes. Lecturers from numerous hospitals using radioisotopes, Oak Ridge National Laboratory and staff members of the Medical and Special Training Division of the Institute will participate. The first week will be devoted to lectures and laboratory work on radioisotopes in therapy and the second with radioisotopes in clinical tracer studies. A limited number of applicants who are able to attend for only one week can be accommodated. A fee of $25 will be charged for the course. Applications are available from Dr. Ralph T. Overman, chairman, Special Training Division, Oak Ridge Institute of Nuclear Studies, P. O. Box 117, Oak Ridge.

CANADA

Eye Bacteriology Laboratory.—An eye bacteriology laboratory has been established by the Banting Institute in the Department of Ophthalmology, University of Toronto. The laboratory is under the direction of Dr. Hugh L. Ormsby. Ophthalmologists may refer their private patients to the laboratory for bacteriologic investigation.

Medical Examinations and Licensure

COMING EXAMINATIONS AND MEETINGS

EXAMINING BOARDS IN SPECIALTIES

AMERICAN BOARD OF ANESTHESIOLOGY: *Written.* July 20. Given simultaneously in several cities in the United States. Final date for filing application is Jan. 20. *Oral.* Coronado, Calif., April 4-7 and Memphis, Oct. 14-17. Sec., Dr. Curtiss B. Hickcox, 80 Seymour St., Hartford 15, Conn.

AMERICAN BOARD OF NEUROLOGICAL SURGERY: *Oral.* Chicago, May 1951. Sec., Dr. W. J. German, 789 Howard Ave., New Haven 4, Conn.

AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY: Part 1, Written Examination and Review of Case Histories. Various locations. Feb. 2, 1951. Final date for filing applications was Nov. 5. *Oral.* New York City, May 10-16. Final date for filing application is Feb. 2. Sec., Dr. Paul Titus, 1015 Highland Building, Pittsburgh 6, Pa.

AMERICAN BOARD OF OPHTHALMOLOGY: *Written.* Various Centers, Jan. 5-6, 1951. *Oral.* San Francisco, March 11-15; New York, May 31-June 5; Chicago, October 8-13. Sec., Dr. Edwin B. Dunphy, 56 Ivie Road, Cape Cottage, Maine.

AMERICAN BOARD OF ORTHOPAEDIC SURGERY: *Part II.* Chicago, Jan. 25-26. Final date for filing applications was Aug. 15, 1950. Final date for receipt of Part I applications for 1951 is Dec. 30, 1950. Sec., Dr. Harold A. Sofield, 122 So. Michigan Ave., Chicago 3.

AMERICAN BOARD OF OTOLARYNGOLOGY: *Written.* New York, Jan. 8-11, 1951. *Oral.* Richmond, Va., May 1-5. Sec., Dr. Dean M. Lierle, University Hospital, Iowa City.

AMERICAN BOARD OF PATHOLOGY: *Written and Oral. Pathological Anatomy and Clinical Pathology.* Cleveland, April 23-24. Final date for filing application is March 15. Sec., Dr. Robert A. Moore, 1402 S. Grand Blvd., St. Louis.

AMERICAN BOARD OF PEDIATRICS: *Written.* Jan. 19. Under local monitors. Only written examination to be given during 1951. *Oral.* New Orleans, March 2-4. Ex. Sec., Dr. John McK. Mitchell, 6 Cushman Road, Rosemont, Pa.

AMERICAN BOARD OF PROCTOLOGY: *Part I in Anorectal Surgery and Proctology.* Kansas City, Minneapolis, Philadelphia and San Francisco, May 12. Sec.-Gen., Dr. Louis A. Buie, 102-110 Second Ave., S.W., Rochester, Minn.

AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY: New York, Dec. 18-19. Final date for filing applications was Sept. 1. Sec., Dr. Francis J. Braceland, 102-110 Second Ave., S.W., Rochester, Minn.

AMERICAN BOARD OF RADIOLOGY: *Oral.* Atlantic City, June 5-9. Sec., Dr. B. R. Kirklin, 102-110 Second Ave., S.W., Rochester, Minn.

AMERICAN BOARD OF SURGERY: *Written.* Various centers, March 1951. Final date for filing applications was Dec. 1, 1950. *Written.* Various centers, Oct. 1951. Final date for filing applications is July 1. Sec., Dr. J. Stewart Rodman, 225 South 15th Street, Philadelphia.

BOARD OF THORACIC SURGERY: *Written.* Various Centers, Feb. 17. Final date for filing application is Feb. 1. *Oral.* New York City, April 19. Sec., Dr. William M. Tuttle, 1151 Taylor Ave., Detroit.

AMERICAN BOARD OF UROLOGY: Chicago, Feb. 10-14, 1951. Final date for filing applications was Sept. 1, 1950. Chicago, Feb. 9-13, 1952. Final date for filing applications is Sept. 1. Sec., Dr. Harry Culver, 314 Corn Exchange Bldg., Minneapolis 15.

Coming Medical Meetings

American Academy of Allergy, Hotel Statler, New York, Feb. 5-7. Dr. Walter S. Burrage, 208 E. Wisconsin Ave., Milkaukee 2, Secretary.

American Academy of Orthopaedic Surgeons, Palmer House, Chicago, Jan. 27-Feb. 1. Dr. Harold B. Boyd, 122 S. Michigan Ave., Chicago 3, Secretary.

American Society for Surgery of the Hand, Palmer House, Chicago, Jan. 26. Dr. Joseph H. Boyes, 1401 S. Hope St., Los Angeles 15, Secretary.

Atlanta Graduate Medical Assembly, Municipal Auditorium, Atlanta, Ga., Feb. 5-7. Mrs. Stewart R. Roberts, 768 Juniper St. N.E., Atlanta, Executive Secretary.

International Post-Graduate Medical Assembly of Southwest Texas, Municipal Auditorium, San Antonio, Jan. 23-25. Dr. John H. Hinchey, P. O. Box 2445, San Antonio 6, Secretary.

Puerto Rico, Medical Association of, Santurce, Dec. 13-17. Dr. Victor J. Montilla, P. O. Box 3866, Santurce 29, Secretary.

DEATHS

Shurly, Burt Russell ⊕ Detroit; born in Chicago, July 4, 1871; Detroit College of Medicine, 1895; did postgraduate work at the University of Vienna; professor emeritus of otolaryngology at Wayne University College of Medicine, formerly known as the Detroit College of Medicine, which he joined in 1896, serving as instructor, lecturer in physiology, professor of otolaryngology and at one time dean; veteran of the Spanish-American War; for many years chief surgeon of the Michigan Naval Reserve; during World War I was in command of Base Hospital No. 36, American Expeditionary Forces stationed in Vittel, France, and was cited by General Pershing for his army service; later a colonel in the medical reserve corps; awarded the Purple Heart and the Legion of Honor; secretary of the Section on Laryngology, Otology and Rhinology from 1911-1913 and chairman 1913-1914 and from 1922 through 1948; member of the House of Delegates of the American Medical Association; past president of the American Laryngological Association, American Laryngological, Rhinological and Otological Society and the American Academy of Ophthalmology and Otolaryngology, which awarded him its gold medal; past president of the Detroit Academy of Medicine; fellow of the American College of Physicians and member of the American Climatological Association; fellow and formerly member of the board of governors of the American College of Surgeons; past president of the Detroit Chapter of the Association of Military Surgeons of the United States; past commander of the Detroit Chapter of Military Order of the World War; for many years member of the board of education, of which he had been president; a member of the board of directors and vice president of the American Board of Otolaryngology from 1930 to 1945; chief of staff, Shurly Hospital; president of Detroit Tuberculosis Sanitarium; consulting otolaryngologist at Woman's Hospital, Receiving Hospital and Harper Hospital, where he died October 20, aged 79, of coronary sclerosis and diabetes mellitus.

Brown, Percy ⊕ Egypt, Mass.; born in Cambridge, Nov. 24, 1875; Harvard Medical School, Boston, 1900; completed internship at Children's Hospital in Boston; in 1903 organized x-ray departments at the Children's Hospital and Carney Hospital in Boston and in 1904 inaugurated x-ray service at the Long Island Hospital and at St. Elizabeths' Hospital in Boston; in 1903 served as an assistant in the use of the roentgen ray at his alma mater; member of the American Roentgen Ray Society, of which, after serving in various official capacities, he became president in 1911 and in 1939 was awarded its president's medal; past president of the Radiological Society of North America, which in 1922 awarded him the gold medal for his research in roentgen diagnosis and therapy; fellow of the American College of Physicians and the American College of Radiology; member of the New York Roentgen Society, Philadelphia Roentgen Ray Society, New England Roentgen Ray Society, the original Roentgen Society of London and before World War I the Deutsche Roentgen Geselleschaft of Berlin; served during World War I as a major in the medical corps, U. S. Army, with Base Hospital No. 5 in France; specialist certified by the American Board of Radiology; variously associated, as radiologist, with the Jackson Clinic, Madison, Wis., the Grunow Clinic of Phoenix, Ariz., the Western Pennsylvania Hospital of Pittsburgh and St. Luke's Hospital in New York; author of a monograph (1935) on "American Martyrs to Science Through Roentgen Rays"; died October 8, aged 74, of hypertensive heart disease.

Cottis, George W., Jamestown, N. Y.; born in Guelph, Canada, March 18, 1880; Cornell University Medical College, New York, 1904; specialist certified by the American Board of Surgery; past president of the Medical Society of the State of New York; past president of the Jamestown and Chautauqua County Medical societies; fellow of the American College of Surgeons; a captain overseas in the Royal Army Medical Corps during World War I; in 1928 member of the House of Delegates of the American Medical Association; served on the staffs of Jamestown General and Woman's Christian Association hospitals; formerly chairman of the New York State governor's committee on public health and of the board of visitors of the State Institute for the Study of Malignant Diseases in Buffalo; associate editor of the *New York State Journal of Medicine* from November 1944 to December 1945; past president of the local Chamber of Commerce; died in St. Cloud, Fla., October 19, aged 70, of coronary occlusion.

⊕ Indicates Fellow of the American Medical Association.

Brunn, Harold ⊕ San Francisco; born in San Bernardino, Calif., in 1874; University of Pennsylvania Department of Medicine, Philadelphia, 1895; an Associate Fellow of the American Medical Association; member of the founders group of the American Board of Surgery; clinical professor of surgery, emeritus, at the University of California Medical School in San Francisco; chairman of the Section on Surgery, General and Abdominal, American Medical Association, 1933-1934; member of the American Surgical Association, Pacific Coast Surgical Association and the American Association for Thoracic Surgery, of which he had been a past president; fellow of the American College of Surgeons; established the Harold Brmn Cardio-Vascular Research Institute; served as surgeon in chief at San Francisco Hospital, University of California Service and was chief of surgical service at Mount Zion Hospital; in 1942 50 pupils and friends dedicated a book to him; died October 5, aged 76.

Levenson, Walter Sabin ⊕ Boston; Harvard Medical School, Boston, 1922; specialist certified by the American Board of Surgery; president of the Greater Boston Medical Society; member of the New England Pediatric Society; fellow of the American College of Surgeons; during World War II served as a commander in the U. S. Navy Reserve and was decorated with the Navy Bronze Medal for service in the Philippine invasion; instructor in surgery, Tufts College Medical School and assistant in surgery at Harvard Medical School; on the staffs of the Beth Israel Hospital, Boston Dispensary and Boston Floating Hospital; died in New York University Hospital in New York September 22, aged 52, of carcinoma of the liver.

Dye, William Joseph Paul ⊕ Wolfeboro, N. H.; born in Sistersville, W. Va., Nov. 10, 1902; Harvard Medical School, Boston, 1925; secretary of the Carroll County Medical Society; vice president of the New Hampshire Medical Society; secretary-treasurer of the New Hampshire Surgical Club; certified by the National Board of Medical Examiners; specialist certified by the American Board of Surgery; member of the New England Obstetrical and Gynecological Society and the New England Surgical Society; chairman of the state board of registration in medicine; on the staff of Huggins Hospital, where he died October 17, aged 47, of coronary thrombosis.

Getchell, Albert Colby, Worcester, Mass.; born in Waterville, Maine, July 9, 1857; Jefferson Medical College of Philadelphia, 1885; member of the American Medical Association; for many years president of the Worcester Tuberculosis Relief Association; fellow of the American College of Surgeons; served on the staffs of Belmont, Memorial and Worcester City hospitals; consulting laryngologist and trustee, Rutland, (Mass.) State Sanatorium; consulting physician, Hospital Cottages for Children in Baldwinsville; organized the Worcester District Medical Library, serving as its librarian for many years; died in Princeton October 1, aged 93, of senility.

Kidner, Frederick Clinton ⊕ Detroit; born in Ipswich, Mass., April 13, 1879; Harvard Medical School, Boston, 1904; emeritus professor of clinical orthopedic surgery at Wayne University College of Medicine; specialist certified by the American Board of Orthopaedic Surgery; member of the American Orthopedic Association, of which he had been president, Clinical Orthopedic Society and the American Academy of Orthopaedic Surgeons; fellow of the American College of Surgeons; affiliated with Children's Hospital of Michigan, Woman's Hospital, Receiving Hospital and Harper Hospital, where he died October 20, aged 71.

Bosworth, Boardman Marsh ⊕ Bronxville, N. Y.; born in New York June 7, 1898; Columbia University College of Physicians and Surgeons, New York, 1931; specialist certified by the American Board of Surgery; certified by the National Board of Medical Examiners; member of the American Association for the Surgery of Trauma; fellow of the American College of Surgeons; served during World War II; affiliated with Lawrence Hospital in Bronxville, Grasslands Hospital in Valhalla, Mount Vernon (N. Y.) Hospital and New York City Hospital; killed near Hainesville, N. J., October 9, aged 52, in a private airplane crash.

Lynch, Charles Francis ⊕ Springfield, Mass.; born in Waltham, Mass., in 1871; New York University Medical College, New York, 1897; an Associate Fellow of the American Medical Association; fellow of the American College of Surgeons; served overseas during World War I; at one time member of the state public health council; formerly chairman

of the police commission; senior surgeon, Mercy Hospital; consulting surgeon, Health Department Hospital in Springfield, Wing Memorial Hospital in Palmer and Amherst College Infirmary in Amherst; died in Mercy Hospital September 27, aged 79, of coronary thrombosis.

Lee, Thomas Benjamin ✦ Collingswood, N. J.; born in 1881; Jefferson Medical College of Philadelphia, 1905; past president of the Camden County Medical Society and the New Jersey State Department of Health; formerly trustee of the New Jersey State Medical Society; specialist certified by the American Board of Obstetrics and Gynecology; fellow of the American College of Surgeons; consulting gynecologist, Zurbrugg Memorial Hospital, Riverside, Salem County Memorial Hospital, Salem, Underwood Hospital, Woodbury and the Cooper Hospital in Camden, where he died October 17, aged 69.

Parowski, Stephen Anthony ✦ Assistant Surgeon Lieutenant (jg) U. S. Navy, retired, San Diego, Calif.; born in Chicago Aug. 31, 1899; Rush Medical College, Chicago, 1927; served during World War I; entered the U. S. Navy June 30, 1925; retired March 31, 1928 for incapacity resulting from an incident of the service; fellow and past president of the American College of Chest Physicians; member of the American Trudeau Society; on the staffs of Mercy, Quintard and Balboa hospitals and Rest Haven Preventorium; died October 7, aged 51.

Alguire, Annie Bell McCallum ✦ Belvidere, Ill.; Trinity Medical College, Toronto, Canada, 1895; formerly member of the county school board; affiliated with Highland and St. Joseph's hospitals; died October 8, aged 82, of hypertension and cerebral hemorrhage.

Andres, Francis Anthony ✦ Allegany, N. Y.; Georgetown University School of Medicine, Washington, D. C., 1931; served during World War II; physician at St. Bonaventure's (N. Y.) College; on the staffs of Olean General Hospital and St. Francis Hospital in Olean, where he died October 21, aged 46, of coronary insufficiency.

Aptaker, Albert J., ✦ Forest Hills, N. Y.; University of Maryland School of Medicine, Baltimore, 1927; associate attending physician on the medical staff of Queens General Hospital in Jamaica; died October 19, aged 47, of coronary occlusion.

Benson, Otis Otto Sr., Minneapolis; Keokuk (Ia.) Medical College, 1898; Rush Medical College, Chicago, 1902; formerly associated with the Indian Service; died October 16, aged 83, of uremia.

Brisbine, Royal Ellis ✦ Burbank, Calif.; State University of Iowa College of Medicine, Iowa City, 1906; affiliated with Behrens Memorial Hospital and Glendale Sanitarium and Hospital, where he died September 30, aged 70, of coronary occlusion.

Brown, Edwin Martin, Washington, N. C.; Bellevue Hospital Medical College, New York, 1896; member of the American Medical Association; past president of the Beaufort County Medical Society; received a citation for service rendered as examiner for the county selective board in World Wars I and II; served as county health officer; affiliated with Fowle Memorial Hospital; died September 28, aged 77, of coronary thrombosis.

Buchanan, John Roosevelt ✦ Youngstown, Ohio; State University of Iowa College of Medicine, Iowa City, 1925; member of the American Academy of Orthopaedic Surgeons; specialist certified by the American Board of Orthopaedic Surgery; served during World War II; on the staff of Youngstown Hospital; died October 19, aged 49, of carcinoma of the pancreas.

Budau, John Harry Diederichs, Milford, Conn.; Yale University School of Medicine, New Haven, 1900; member of the American Medical Association; died in Bridgeport August 21, aged 75, of rupture of an abdominal arteriosclerotic aneurysm.

Burt, Lawrence William, New Orleans; Tulane University of Louisiana School of Medicine, New Orleans, 1936; member of the American Medical Association; served during World War II; affiliated with Touro Infirmary; died September 29, aged 40.

Ciolli, Dominic Trinity ✦ Buffalo; University of Buffalo School of Medicine, 1920; member of the American Psychiatric Association; affiliated with Edward J. Meyer Memorial, Deaconess, Sisters of Charity and Buffalo Columbus hospitals; died in the township of Holland, N. Y., October 22, aged 55, of coronary disease.

Clendenen, Charles M., Damascus, Va.; University College of Medicine, Richmond, 1910; president of the Bank of Damascus; died in the George Ben Johnston Hospital, Abingdon, September 29, aged 66, of congestive heart failure.

Cogswell, John Wilkinson, Strasburg, Ohio; State University of Iowa College of Homeopathic Medicine, Iowa City, 1906; member of the American Medical Association; served during World War I; on the associate staff of the Massillon (Ohio) Hospital and Union Hospital in Dover, where he died October 9, aged 67, of heart disease.

Crossland, John R. A., St. Joseph, Mo.; Meharry Medical College, Nashville, Tenn., 1890; died in State Hospital No. 2, September 13, aged 86.

Cush, Thomas James ✦ Johnstown, Pa.; Jefferson Medical College of Philadelphia, 1924; fellow of the American College of Surgeons; president of the Cambria County Medical Society; chief of orthopedic surgery at Mercy Hospital; a member of the reserve staff of the Conemaugh Valley Memorial Hospital, where he died September 30, aged 49, of coronary occlusion.

Davis, Albert Wellington ✦ Kansas City, Mo., Kansas City Medical College, 1902; formerly on the staff of St. Luke's Hospital, where he died October 4, aged 87, of complications following a fractured hip received in a fall.

de la Pila Iglesias, Manuel, Ponce, P. R.; Universidad de Barcelona Facultad de Medicina, Spain, 1906; past president of the Porto Rico Medical Association; fellow of the American College of Physicians; member of House of Delegates of the American Medical Association in 1940, 1941, 1946 and 1947; medical director of the Clinica Quirurgica Dr. Pila; killed October 7, aged 66, in an automobile accident.

Dodge, Charles Harwood, Clinton, Wis.; Marquette University School of Medicine, Milwaukee, 1913; served in France during World War I; health officer of Clinton township; formerly member of the school board; died in Wisconsin General Hospital, Madison, September 8, aged 59, of coronary thrombosis.

Dryfuss, Barney Joachim ✦ New York; University of Louisville (Ky.) Medical Department, 1903; Cornell University Medical College, 1906; formerly on the faculty of Cornell University Medical College; on the staff of St. Clare's Hospital, where he died October 14, aged 71, of dissecting aneurysm.

Duncan, Oscar Allen, Fort Leavenworth, Kan.; St. Louis University School of Medicine, 1905; civilian physician for the Army at Fort Leavenworth; died in the U. S. Army Hospital October 3, aged 70, of progressive muscular atrophy.

Dunkley, David A., Roanoke, Va.; University College of Medicine, Richmond, 1910; member of the American Medical Association; affiliated with Shenandoah Hospital, where he died September 26, aged 67, of thrombophlebitis with multiple pulmonary emboli.

Dunlay, Emmett Blaine, Watertown, N. Y.; University of Buffalo School of Medicine, 1920; member of the American Medical Association; served as medical school inspector for the public school system in Watertown; formerly on the staffs of the House of the Good Samaritan and Mercy Hospital; died recently, aged 57.

Evans, Evan Albert, Rosedale, Ind.; Indiana Medical College, School of Medicine of Purdue University, Indianapolis, 1906; affiliated with Vermillion County Hospital in Clinton; died in St. Anthony's Hospital, Terre Haute, October 16, aged 71, of cerebral hemorrhage and hypertension.

Felberbaum, David ✦ New York; Columbia University College of Physicians and Surgeons, New York, 1906; affiliated with Montefiore and Mount Sinai hospitals; died October 26, aged 67, of cerebral thrombosis.

Fitch, Josiah Whitaker, Louisville, Ky.; University of Louisville Medical Department, 1907; member of the American Medical Association; died in Jewish Hospital, September 22, aged 70, of gastric ulcer.

Fitch, Stewart Jackson, Laguna Beach, Calif.; the Hahnemann Medical College and Hospital, Chicago, 1914; served during World War I; died September 26, aged 65, of arteriosclerosis and edema of brain.

Fledderjohann, Henry E., New Knoxville, Ohio; University of Pennsylvania Department of Medicine, Philadelphia, 1886; died in Dayton October 2, aged 94, of chronic myocarditis.

Fraser, Stuart Evans, North Miami, Fla.; the Hahnemann Medical College and Hospital, Chicago, 1917; died in Duke Hospital, Durham, N. C., October 5, aged 64, of arteriosclerosis with gangrene of both legs.

Gabel, William Jacob, Syracuse, N. Y.; Syracuse University College of Medicine, 1916; served on the staff of the Hospital of the Good Shepherd, where he died October 15, aged 60, of cardiac decompensation.

Gaines, Frank McFarland, Carrollton, Ky.; Kentucky School of Medicine, Louisville, 1893; formerly associated with the U. S. Public Health Service Reserve and was on the staffs of various Veterans Administration hospitals; served during World War I; died October 5, aged 80, of coronary occlusion.

Garman, Russell Arthur ✦ Jeannette, Pa.; Jefferson Medical College of Philadelphia, 1930; past president of the Westmoreland County Medical Society; served during World War II; was shot and killed by a former patient October 1, aged 46.

Gershenson, Edward Harry, New York; Long Island College Hospital, Brooklyn, 1905; died in Beekman Hospital October 5, aged 68, of cerebral accident.

Goldsmith, Leon Albert ✦ Portland, Ore.; Harvard Medical School, Boston, 1922; assistant clinical professor of cardiology at the University of Oregon Medical School; specialist certified by the American Board of Internal Medicine; member of the North Pacific Society of Internal Medicine; fellow of the American College of Physicians; affiliated with Multnomah Hospital; died in Chicago November 2, aged 53, of coronary heart disease.

Grace, James Joseph, Springfield, Mass.; Middlesex College of Medicine and Surgery, Cambridge, 1933; member of the American Medical Association; school physician; served in the Pacific area during World War II; affiliated with Mercy Hospital; died October 17, aged 44, of carcinoma of the rectum.

Griffith, Guy Everett ✦ Tacoma, Wash.; Northwestern University Medical School, Chicago, 1920; died in Santa Monica, Calif., October 13, aged 61, of cerebral vascular accident and coronary occlusion.

Grover, Joseph Isaac ✦ Quincy, Mass.; Harvard Medical School, Boston, 1911; an Associate Fellow of the American Medical Association; affiliated with Quincy City Hospital; died October 19, aged 65, of carcinoma of the duodenum.

Hapeman, Harry, Minden, Neb.; Rush Medical College, Chicago, 1882; fellow of the American College of Surgeons; died October 29, aged 92, of uremia.

Harrison, William H., Kokomo, Ind.; Medical College of Indiana, Indianapolis, 1896; member of the American Medical Association; past president of the Howard County Medical Society; died October 23, aged 85, of cerebral hemorrhage and arteriosclerosis.

Hazlett, Almon Cyrus ✦ Wyoming, Pa.; Jefferson Medical College of Philadelphia, 1913; served with the American Expeditionary Forces overseas during World War I; past president of the Luzerne County Medical Society; affiliated with Nesbitt Memorial Hospital in Kingston and Pittston (Pa.) Hospital; died in Philadelphia October 17, aged 59, of ruptured aneurysm of the circle of Willis.

Hogan, Stephen Clement ✦ Chicago; Chicago College of Medicine and Surgery, 1912; died October 31, aged 67, of cerebral hemorrhage and hypertensive heart disease.

Jacobs, Francis Edward ✦ San Diego, Calif.; University of Oregon Medical School, Portland, 1929; past president of the San Diego County Medical Society; served on the staffs of San Diego County and Quintard hospitals; died in Woodland Clinic Hospital, Woodland, October 14, aged 47, of coronary occlusion.

Kenkel, Henry Frank, Cincinnati; University of Cincinnati College of Medicine, 1920; died October 19, aged 56, of acute coronary occlusion.

Koempel, Franz, New York; Julius-Maximilians-Universität Medizinische Fakultät, Würzburg, Bavaria, Germany, 1893; died October 31, aged 80.

Lasher, Earl Parsons, Newtown, Conn.; Albany (N. Y.) Medical College, 1898; formerly affiliated with the New York Eye and Ear Infirmary in New York; died in the Danbury (Conn.) General Hospital October 28, aged 77, of cerebral hemorrhage and pulmonary embolism.

Liles, Homer D., Flowery Branch, Ga.; Georgia College of Eclectic Medicine and Surgery, Atlanta, 1913; served during World War I; died in Hall County Memorial Hospital, Gainesville, October 20, aged 61, of cardiac asthma.

Mack, Gertrude Griswold, New York; New York Medical College and Hospital for Women, Homeopathic, New York, 1897; died recently, aged 77, of coronary thrombosis.

McCord, James Bennett, Oakham, Mass.; Northwestern University Medical School, Chicago, 1894; for many years medical missionary of the American Board of Foreign Missions in Africa and founder of the McCord Zulu Hospital, the first hospital for Africans in Natal Province; died October 5, aged 80, of heart disease.

McCoy, Earl Tucker, Los Angeles; College of Physicians and Surgeons, Los Angeles, 1918; member of the American Medical Association; formerly on the staff of the Methodist Hospital of Southern California; died September 14, aged 65, of coronary thrombosis.

McMahan, Asher Reid, Memphis, Tenn.; Rush Medical College, Chicago, 1908; member of the American Medical Association; served on the staffs of Gartly-Ramsay, Baptist, St. Joseph and Methodist hospitals; medical director of the Columbian Mutual Life Insurance Company; died in Baptist Hospital October 17, aged 67, of carcinoma of the prostate.

Macon, Gideon Hunt, Warrenton, N. C.; University College of Medicine, Richmond, 1910; member of the American Medical Association; served as vice president of the Medical Society of the State of North Carolina; died in Park View Hospital, Rocky Mount, October 1, aged 63, of coronary occlusion.

Meck, Henry Lehr, Dundee, Mich.; Detroit College of Medicine, 1910; member of the American Medical Association; served during World War I; on the staff of Mercy Hospital, Monroe; for many years president of the Monroe County Bank; died in Ontario, Canada, October 4, aged 65, of heart disease.

Mullins, Charles Ellison ✦ Meadville, Miss.; Memphis (Tenn.) Hospital Medical College, 1909; served as vice president of the Mississippi State Medical Association; county health officer; died in King's Daughters Hospital, Brookhaven, September 22, aged 66, of acute cardiac failure.

Munn, Jesse Adolphas ✦ McAlester, Okla.; University of Arkansas School of Medicine, Little Rock, 1910; served during World War I; associated with St. Mary's and Albert Pike hospitals; died August 27, aged 67, of coronary embolism.

Resnisky, Andrew Francis, Hartford, Conn.; Georgetown University School of Medicine, Washington, D. C., 1923; fellow of the American College of Surgeons; on the staff of St. Francis Hospital; died in Windham Memorial Hospital in Willimantic, September 28, aged 52, of coronary thrombosis.

Rogers, James Coburn, Bellefonte, Pa.; University of Pennsylvania Department of Medicine, Philadelphia, 1905; school physician; on the staff of Centre County Hospital; died in Philipsburg (Pa.) State Hospital September 29, aged 66, of arteriosclerotic heart disease.

Schoolman, Noah, Chicago; Jefferson Medical College of Philadelphia, 1903; formerly associated with the Illinois Charitable Eye and Ear Infirmary; died October 21, aged 75, of arteriosclerotic heart disease.

Siefert, John Frederick, Detroit; University of Michigan Department of Medicine and Surgery, Ann Arbor, 1888; died October 13, aged 88, of bronchopneumonia and cerebral thrombosis.

Taylor, Emora Arthur, Gulfport, Miss.; Leonard Medical School, Medical Department Shaw University, Raleigh, N. C., 1906; affiliated with Memorial Hospital; died September 13, aged 70, of cerebral hemorrhage and arteriosclerosis.

Twitchell, Edward Woodland, San Francisco; Cooper Medical College, San Francisco, 1892; specialist certified by the American Board of Psychiatry and Neurology; member of the American Medical Association; clinical professor of psychiatry emeritus at University of California Medical School; died September 2, aged 78, of cerebral hemorrhage.

Valentine, Clarence Medbery ✦ Columbus, Ohio; Starling Ohio Medical College, Columbus, 1908; served during World War I; first health commissioner of Franklin County; affiliated with Mercy Hospital, St. Ann's Maternity Hospital and the Grant Hospital, where he died October 2, aged 67, of coronary thrombosis.

Wallace, George Sellers, Hilliard, Fla.; Jefferson Medical College of Philadelphia, 1897; member of the Medical Society of the State of Pennsylvania and the American Medical Association; died in Lake City, September 26, aged 81, of carcinoma of the prostate.

Weber, Burghard Andrew, Milwaukee; Wisconsin College of Physicians and Surgeons, Milwaukee, 1898; died in Milwaukee County Hospital August 26, aged 76, of coronary thrombosis and diabetes mellitus.

FOREIGN LETTERS

LONDON

(From a Regular Correspondent)

Oct. 16, 1950.

Trend in Modern Surgery

Recently the London *Times* reported a speech given by Sir Cecil Wakeley, president of the Royal College of Surgeons, London, when he gave the inaugural address to the Westminster Medical School at Church House, Westminster, London. He said that there seemed to be a tendency for teachers to specialize in a small aspect of surgery and beat it until it was dead and to take teaching away from those who were practicing surgery as a full time occupation. The latter, he said, were the very persons who were continually in touch with patients and their diseases and, therefore, were perhaps better able to teach, because of their more practical and less academic knowledge. He said there was a danger of ultraspecialization, when men would perform only one type of operation. Such a state of affairs was bad for teaching and made for little progress. It was important that teaching hospital surgeons should remain general surgeons, but, on the other hand, it did not matter if they had a specialty, for instance, gastric surgery, thyroid surgery or urological surgery.

There was also a tendency for some workers to overlook clinical observation and to rely too much on roentgenograms and pathological or biochemical tests in making a diagnosis. He doubted whether the clinician of today had the clinical acumen of the late Victorian physicians, who used few tests and in many instances were extraordinarily accurate in their diagnosis. He mentioned the new Medical Act and hoped that when it came into force, making a year's postgraduate experience compulsory before registration, the qualified student would be able to take part of his year's postgraduate training with a general practitioner. Surgery had by no means arrived at its zenith, and further progress was not impossible, although it might well be that future research would eliminate some forms of surgical operations and that some disease which had been treated by surgical intervention would be cured by intravenously administered drugs. Sir Cecil Wakeley, who presented the prizes, was welcomed by Mr. H. M. Clowes, chairman of Westminster Medical School.

Smoking and Carcinoma of the Lung

A preliminary report on smoking and carcinoma of the lung, by Drs. Richard Doll and A. Bradford Hill, appeared in the December 9 issue of the *British Medical Journal*. It states that the great increase in the number of deaths attributed to cancer of the lung in the last 25 years justifies the search for a cause in the environment. The authors investigated the possible association of carcinoma of the lung with such factors as smoking, exposure to car and fuel fumes and occupation.

The material for the investigation was obtained from 20 hospitals in London. Social workers visited and interviewed each patient. Patients with stomach or large bowel carcinoma and a noncancer control group, comparable in age and sex with the patients with lung cancer, served for comparison. A group of 649 men and 60 women with carcinoma of the lung were interviewed. Three-tenths per cent of the men and 31.7 per cent of the women were nonsmokers. The corresponding figures in the noncancer control groups were 4.2 per cent for the men and 53.3 per cent for the women. Twenty-six per cent of the male and 14.6 per cent of the female patients with lung cancer smoked the equivalent of 25 or more cigarets a day prior to their illness, while only 13.5 per cent of the male and none of the female noncancer control patients smoked as much. Similar differences were found when comparisons were made between the maximum amounts ever smoked and the estimated total amounts ever smoked. Cigaret smoking was more closely related to carcinoma of the lung than pipe smoking. No distinct association was found with inhaling. Taken as a whole, the patients with lung cancer had begun to smoke earlier and had continued for longer periods than the controls; the differences, however, were not statistically significant. Rather fewer patients with lung cancer had given up smoking.

The possibility of unreliable results was considered—those that could be due to the selection of an unsuitable group of control patients, or patients having respiratory disease exaggerating their smoking habits, or bias on the part of the interviewers. Care was taken to eliminate all these fallacies.

From consideration of smoking histories of patients without cancer of the lung, a tentative estimate was made of the number of persons who smoked different amounts of tobacco in Greater London, and the relative risks of development of the disease among different grades of smokers were calculated. Speculative figures only were obtained, and it is suggested that above the age of 45 the risk of having the disease increases in simple proportion with the amount smoked, and it may be 50 times as great among those who smoke 25 or more cigarets a day as among nonsmokers. The authors observed sex ratio among nonsmokers (based, it must be stressed, on very few cases), saying the ratio can be readily accounted for if the true incidence among nonsmokers is equal in both sexes. It is not possible to deduce a simple time relation between the increased consumption of tobacco and the increased number of deaths attributed to cancer of the lung. It may possibly be due to improved diagnosis, and it may be because the carcinogen in tobacco smoke is introduced into the tobacco during its cultivation or preparation. Greater changes have taken place in the methods involved in these processes than in the actual amount of tobacco consumed.

Disordered Society

During his work in an international organization for the care of refugees R. N. Tronchin-James observed interesting patterns of human behavior in the insecure and disordered world of today. The refugee is the physical example of the insecurity that may overtake anyone. Observations made over 18 months on a refugee population of 30,000 in Austria are recorded. Although the population under consideration consisted of persons of every age group and many nationalities, various creeds and different professional, social and economic status, their situation reduced them to a common plight, with similar mental reactions.

The symptoms of more typical reactive or conversion neurosis were not found in this large population. A form of neurosis widespread among the refugees was characterized by emotional shock persisting for years, with suppression of active and aggressive psychic qualities, lack of volition and emotional incapacity to consider the future. There was a positive resistance to change, even though the present was more insecure, uncomfortable and completely different from the previous pattern of life. The physical care was good, and the physical necessity of transporting them to new countries was dealt with energetically and with considerable success.

When such situations are imminent, workers should attempt to restore the refugees to mental health, so that each regains the fullest vigor of his ethnic and individual capacities for dealing with the new situation and environment that he has to face. The capacity for adjustment to a new situation is a criterion of his mental health. To restore to the refugee the fullest enjoyment of that capacity should be the primary aim and would decrease enormously the amount of purely supportive work that has to be done.

TURKEY

(From a Regular Correspondent)

ANKARA, Oct. 28, 1950.

Eleventh National Medical Congress

This congress was held at Ankara Oct. 16-19, 1950, under the auspices of Celal Bayar, president of Turkey, and with Adnan Menderes, the prime minister, as honorary president. It was attended by almost 700 members from all parts of the country. Dr. Ekrem Hayri Üstündag, minister of health and social assistance, opened the congress. The topic was tuberculosis.

Ord. Prof. Tevfik Saglam of Istanbul University, Turkey's foremost authority on tuberculosis, spoke on tuberculosis control in Turkey; Dr. Tevfik Ismail Gökee, chief of the Istanbul Heybeliada Tuberculosis Sanatorium, on the positive results of antibiotic therapy; Dr. Etienne Berthet, consultant of tuberculosis for the World Health Organization, rehabilitation, reeducation and the medicosocial aspects of tuberculosis; Dr. Ihsan Rifat Sabar, tuberculosis control in other countries; Prof. Nusret Karasu, the source of tuberculosis infection and its effects and on the result of BCG vaccination of primary school children in Ankara; Dr. Ahmed F. Erbelger, cavernostomy, tamponade and extrapleural pneumothorax; Dr. Sacit Tezelli, the result of extrapleural collapse therapy in pulmonary tuberculosis; Dr. Turgut Targay, the role of pneumoperitoneum in the treatment of tuberculosis; Dr. Yakup Çelebi, chief of the Istanbul-Haydar Pasha Tuberculosis Hospital, the epidemiology of tuberculosis; Dr. Nureddin Onur, the results of BCG vaccination in Istanbul; Dr. Sebib Say, the result of BCG vaccination in infants, preschool and school children in Izmir; Ord. Prof. Mazhar Osman Uzman and Prof. Ihsan Sukri Aksel, psychological symptoms in the course of tuberculosis meningitis; Dr. (V.M.D.) R. Üner and Dr. (V.M.D.) F. Türker, tuberculosis in stray cats; Ord. Prof. Akif S. Shakar, streptomycin therapy in bone and joint tuberculosis; Dr. F. Dikengil, confirmation of bronchial destruction in tuberculous lymphadenopathy by postmortem bronchography; Prof. Nusret Karasu, the army and tuberculosis; Dr. Hasan Fehmi Gökalp, occupational therapy for the tuberculous; Prof. Rasim Adasal, dementia precox and the etiological relation to tuberculosis; Dr. Baha Arkan, school hygiene and tuberculosis; Prof. K. Mutlu, ten years' research on tuberculosis specimens in the pathological anatomy laboratory; Dr. Neşati Üster, tuberculosis in Bursa City and epidemiology; Dr. Orhan Zihni Sanus, increase of tuberculosis in Turkey in relation to standards of living; Prof. N. Karasu, Dr. N. Menemenli and Dr. M. Özköse, glucoregulation in tuberculosis; Dr. Ö. Bican, surgery in pulmonary tuberculosis; Dr. S. Berkman, mass chest examination; Dr. T. Gökce and Dr. S. Velicangil, investigation of bovine type tuberculosis in Turkey; Dr. I. Gürevin, spontaneous hypochloremia and hypochloremic nephropathy in tuberculosis; Dr. N. Tuna, changes in blood circulation in collapse therapy; Dr. A. L. Karan, skin tuberculosis and the skin in tuberculosis; Dr. R. T. Kinacigil, vitamin D_2 therapy in skin tuberculosis, and Prof. Karasu, Dr. Baloglu and Dr. Dülgeroglu, tuberculosis and adrenal function. Forty-three other communications were presented. This congress was accompanied with an exhibit of domestic and foreign pharmaceutical preparations and public health propaganda. After the congress, the health exhibit was open to the public.

At the United States Information Service Library at Ankara an opportunity was provided for the inspection of medical and medicosocial publications. Congress members were presented with a copy of "Books on Science," published by the United States Department of State. The next medical congress is to be held in 1952 at Ankara; the topic will be rheumatism.

Influenza Epidemic

With intermittent local epidemics, widespread epidemics of influenza occur in Turkey about every five years. The last epidemic outbreak in almost all the 63 provinces occurred in January 1949. Starting abruptly in Ankara, it continued for four weeks and subsided suddenly. The incidence was highest in Ankara (25 to 80 per cent); the mortality rate there was comparatively low. There were 126 deaths in the first week, of which 32 were caused by bronchopneumonic complications, 161 deaths in the second week, of which 53 were caused by bronchopneumonic complications, and 127 deaths in the third week, of which 46 were caused by bronchopneumonic complications.

According to investigations by Dr. Sabahaddin Payzin, director of the control laboratory at the Ankara Refik Saydam Institute of Hygiene, and Dr. Sadik Okkan, the serums of all patients had reacted positively to A antigen. A number of cases of highly toxic conditions with such complications as albuminuria, hilar lymphadenia and encephalomeningitis were observed.

Five groups of four mice each were given a nasal inoculation with a throat secretion from five patients. After three days a strain was cultivated. The dried lungs of the mice were crushed in a sterile mortar with sterile sand and penicillin, streptomycin and 5 cc. of sodium chloride solution added. Four other mice were inoculated with this suspension. The second passage caused several deaths. Samples of the fifth strain were sent for control to the World Influenza Central Institute, where Prof. Andrews identified them as an unknown subtype. Inoculations of squirrels also proved the virulence of the virus.

The virus of the Ankara epidemic was not the same as that of the French and Italian epidemics that occurred two months earlier. The Italian virus was the B type; the French type A virus was not exactly like the Ankara virus. The influenza virus type of surrounding countries not having been announced, the virulence of the Ankara endemic virus was possibly the result of mutation. Inoculation of the Refik Saydam Institute of Hygiene personnel with vaccine from the Eli Lilly laboratory proved effective. The following year there was no influenza epidemic in Turkey.

Fourth Turkish Microbiology Congress

Under the presidency of Dr. Ekrem Hayri Üstündag the congress was held on October 18-19 at Ankara. Dr. Nureddin Onur, chief of the Istanbul Hygiene Laboratory, spoke on the results of BCG vaccination in Istanbul; Dr. Sebib Say, on the results of BCG vaccination in Smyrne; Dr. (V.M.D.) Turgud Argun, tuberculosis epidemiology of cows in Turkey; Ord. Prof. Ihsan Hilmi Alantar and his associate Dr. Sezai Bedreddin Tümay of Istanbul University, clinical aspects of toxicosis and therapy and prevention of diarrhea in infants; Dr. N. Fakaçelli of Istanbul, parenteral treatment of infant diarrhea; Dr. Zekai Muammer Tuncman, Istanbul, epidemiology of rabies and precautionary measures in Turkey; Prof. Ihsan Shükrü Aksel of Istanbul University, encephalomeningitis after rabies vaccination, and Ord. Prof. (V.M.D.) Sureyya Aygün, control of rabies in animals. The next congress is to be held in 1952 at Ankara; the topics will be epidemiology and etiology of Q fever, poliomyelitis and tetanus. The seventh National Surgical Congress was held also on October 18; the most important subject was bone tuberculosis, with emphasis on the therapy of tuberculosis of the vertebrae, on which Prof. Hayri Nishantash reported.

Professor Nihad Reshad Belger

The minister of health and social assistance has resigned because of poor health. His successor is Dr. Ekrem Hayri Üstündag. He studied hygiene and bacteriology in Germany for five years and has for many years been active in public health work. He taught at the medical school in Damascus before World War I.

ITALY

(From a Regular Correspondent)

FLORENCE, Sept. 20, 1950.

Natural and Artificial Iodoproteins

Continuing the series of lectures on protein held at the Superior Institute of Public Health, Prof. Jean Roche of the Collège de France discussed natural and artificial iodoproteins. He said that the principal problems of iodine biochemistry in animals are linked to the presence of this element in some proteins, among which are three iodoamino acids, derived from L-thyroxine: 3-monoiodinethyroxine, 3-5-diiodinethyroxine and thyroxine. These substances are formed by halogenation of thyroglobulin in the thyroid of vertebrates and that of scleroprotein in the horny skeleton of invertebrates. The same result may be obtained with artificial halogenation, the biologic activity of the natural and of the artificial iodoproteins being qualitatively identical, except for some differences especially concerning the galactogenous power. Knowledge of the physiological property of the various iodoproteins is of importance for their application in medicine and zootechnics. With a brief survey of the composition and property of thyroglobulin the speaker pointed out that the thyroid effects, in the first stage, the synthesis of these proteins by incorporating tyrosine and, in the second stage, the halogens. Proteidogenesis and iodization are two successive, independent processes; the latter contributes to the formation of thyroxine. The formation of iodoproteins by direct action of the halogen on various substrates, such as casein, insulin and pepsin, has been brought about primarily to obtain products endowed with metabolic activity or antigoitrogenic potency. These, under certain conditions, induce the formation of thyroxine, its quantity being a function of some variables, the most important of which is the structure of the iodonated protein. The physiological activities of the thyroglobulins and of the artificially iodized proteins are manifold and are due to the presence of thyroxine. The study of the intensity of these actions in relation to their content of the hormone has been the subject of many discussions. The results obtained concerning the antigoitrogenic action of iodocasein and thyroglobulin show that the effects observed are not only related to the content of thyroxine and to the degree of assimilation of the latter but to the rapidity of its reabsorption. The author concluded that the biochemistry of natural and artificial iodoproteins is linked to the biochemistry of iodothyroxine and of the thyroxine.

Medicosurgical Society

At a meeting of the Medicosurgical Society of Pisa, Drs. Tangheroni and Bottone discussed methods of diagnosing spasmophilic diathesis and their clinical value. They applied to infants the hypocalcemia and hyperpnea tests, suggested as diagnostic methods for spasmophilia in adults. They combined the humoral investigation on calcium-phosphorus metabolism with the study of chronaxia and recommended the use of these methods for the diagnosis of spasmophilic diathesis.

Dr. Tarantino reported investigations that show how the synthesis of glycogen performed in vitro by the liver of rats treated with pituitary adrenocorticotropic hormone (ACTH) can take place starting from carbohydrates such as glucose, in addition to protein and lipid derivatives.

Dr. Landi surveyed aseptic necrosis of bone, with special reference to the upper epiphysis of the femur, to the scaphoid and the semilunar bones. These osseous alterations, found in numerous clinical forms, such as osteochondritis and the results of trauma, have in common a disturbance of the blood circulation, and they all lead to the final picture of arthrosis deformans.

Drs. Conti and Andreani reported results of their study on lipemic variations produced by the administration of large doses of pituitary adrenocorticotropic hormone or by prolonged administration of this drug for several days. They observed that an intramuscular injection of large doses is followed by hyperlipemic or hypolipemic reactions, closely related to the neuroendoctrine orientation of the patients and to the state of hypophysial function. In patients with clear manifestations of hypopituitarism, there is a constant increase of the total lipids and cholesterols, while rapid diminution of lipids may be observed in patients with hyperpituitarism. The speakers observed a constant diminution of total lipids and cholesterols after a prolonged treatment with pituitary adrenocorticotropic hormone in all cases. The authors are of the opinion that the lipemic and cholesteremic variations induced by adrenocorticotropic stimuli represent manifestations of the general lipid metabolism, induced and sustained by the reactivated function of the adrenal cortex.

Society of Gerontology

The Italian Society of Gerontology and Geriatrics was officially established at a meeting at the Medical Clinic of the University of Florence. Professor Greppi, clinician of Florence, was elected president. The society developed from a group of research workers in this field formed in 1948 through the efforts of Prof. Maurizio Ascoli, clinician of the University of Palermo. The society contributed numerous reports to the First International Congress held at Liège and will participate in the next National Congress of Medicine and Surgery.

BELGIUM

(From a Regular Correspondent)

LIÈGE, Oct. 30, 1950.

Meningitis and Streptomycin

Intensive studies have been devoted to the treatment of tuberculous meningitis with streptomycin. The universities of Brussels (with Dubois, Linz, Van Wien, Govaerts and Durieu), Liège (with Roskam, Plumier, Reginster and their pupils), Louvain (with Van Goidsenhoven and Stevens) and Ghent (with Hooft and Deneve) have contributed to the study of this problem. It seems that there is general agreement that combined treatment by intramuscular and intraspinal or suboccipital injections is important. According to Dubois, this combined treatment with daily intraspinal injection is maintained for 45 days and is followed by a rest period of 20 days. Then follows a second period of 20 days' treatment with daily intramuscular and intraspinal injections and a second rest period of 20 days. The third course consists of treatment for 30 days with intraspinal injections every two days.

In patients undergoing treatment for miliary tuberculosis, the authors performed a spinal puncture every eight days, which sometimes enabled them to detect the meningeal infection before the appearance of the clinical symptoms. In such cases, the combined treatment was instituted and the result of cultures later proved the sound basis of this procedure. Inoculation of guinea pigs, culture of the cerebrospinal fluid and determination of streptomycin levels in the blood and the cerebrospinal fluid were done periodically. The fasting sugar content of the cerebrospinal fluid was determined and then compared with the sugar content of the blood. From these observations during the initial period of the disease, the authors reached the following conclusions: combined treatment arrests the rapid progression of tuberculous meningitis. After the patients have passed the difficult period, the first five months, in which the prognosis is greatly influenced by the early institution of treatment, they show the exterior aspects of convalescence. However, some of these patients are still threatened by serious difficulties, especially by relapse. In addition, the following observations were made: 1. Patients in whom treatment is started more than 15 days after onset have a slight chance of surviving. 2. The existence of paralysis and of a comatose condition at the beginning of

treatment indicates usually a fatal prognosis. 3. Prolonged vomiting during treatment indicates unfavorable extension of the disease.

Hooft and Deneve, on the basis of clinical symptoms and results of examination of the cerebrospinal fluid and the eyegrounds, are in favor of prolonging the treatment in certain cases as long as eight or nine months. Maldague reports the following results. The percentage of apparent cures in a group of 39 children, in whom the treatment was started six to fourteen months prior to reporting, was 51. There were two cases with serious, definitive sequels. The outcome in 8 per cent of the children is still doubtful. The death rate is high during the first month of treatment and decreases considerably after the second month. The prognosis for children under two years is particularly unfavorable. The coexistence of miliary tuberculosis does not seem to aggravate the prognosis of meningitis. In 15 of 18 cases of miliary tuberculosis of the lungs, a complete and seemingly definitive roentgen clearing of the lungs was obtained in one to six months, often even in two or three months. Plumier reported the following results: 38 deaths and 26 survivals. The 26 surviving patients included 16 showing a favorable and six an unfavorable course. Of the 10 patients with associated miliary tuberculosis, nine died and one recovered.

Some authors attributed the failures to the formation and development of fibrinous or fibrocaseous deposits rather than to the acquired streptomycin resistance of the bacilli. Van Goidsenhoven believes that, because of the availability of streptomycin, tuberculous meningitis and miliary tuberculosis are no longer hopeless diseases. The two essential factors for the distant prognosis are: (1) early diagnosis and immediate institution of treatment and (2) prolonged combined treatment with daily intramuscular and intraspinal injections. Relapses after cessation of treatment and the late recurrence of the disease toward the end of the treatment threaten the later prognosis of convalescent patients, but the initial tuberculous localization always constitutes a threat. The more important local complications during the course of intraspinal therapy are meningeal hemorrhage, pachymeningitis and hydrocephalus. The more serious toxic manifestations are auditory and vestibular disturbances. With the dosage used at present, total deafness occurs rarely. A likelier toxic manifestation is insufficiency of renal function caused by abnormally high levels of streptomycin in the blood.

The Red Cross in the Congo

The Red Cross in the Congo, which is a section of the Belgian Red Cross, recently published reports on its activity during 1948 and 1949, which extended to the following spheres: care of lepers, venereal diseases, medical assistance to the indigent, creation and maintenance of training schools for nurses and teaching the essentials of hygiene to the native population. Protection of children is also a large part of its activities. Outpatient consultation services and clinical services have been established for the care of nursing infants. A complete medicosocial service has been established, which has been extended by the creation of a workshop for the mothers of the native population. The workshop makes children's clothes for needy members of the service. That the native women gladly devote part of their time to the Red Cross is an encouraging sign, because the feeling of mutual help and devotion is little developed among natives beyond the restricted circle of the family or of the tribe.

Death of Prof. André Gratia

The death of Professor Gratia has deeply moved the medical profession in Belgium. Just 57 years old, he died while still very active in scientific work. Since 1933, he was professor of bacteriology at the University of Liège and director of the bacteriologic service of Malvoz Institute. As corresponding member of the Royal Academy of Medicine of Belgium, he distinguished himself particularly by his investigations on bacteriophages, plant viruses, immunity to anthrax and antibiotics. In 1946 the government commissioned him to direct a center of research on penicillin in Liège.

COLOMBIA

(From a Regular Correspondent)

Bogotá, Oct. 20, 1950.

Glucose Blood Levels and Phosphoric Esters of Thiamine

Drs. Gonzalo Montes Duque and Julio Cárdenas Araque presented, at the last session of the National Academy of Medicine, September 28, the result of preliminary experiments on glucose levels in man and animals after the administration of the pyrophosphoric ester of thiamine (cocarboxylase) and of the orthophosphate ester of thiamine. Dr. Cárdenas thought that certain disorders of the nervous system, such as schizophrenia, might be due to a disturbance of carbohydrate metabolism of the neurons. The theory is supported by the favorable results obtained by the use of insulin shock in some cases of schizophrenia. The speakers studied the multiple factors which control cerebral metabolism and tried cocarboxylase in the treatment of schizophrenia. Their results suggest that cocarboxylase affects carbohydrate metabolism. They found that administration of cocarboxylase, either orally or intraperitoneally, to mice regularly produced convulsions. Since the pyrophosphoric radical has a hypocalcemic action which might have accounted for the observed convulsions, sodium pyrophosphate was tested on another group of animals. The results were the same; the animals had convulsions. Since the orthophosphoric radical does not cause hypocalcemia, a new compound was synthesized in which the pyrophosphoric radical was replaced by an orthophosphoric radical. Thiamine orthophosphate given intraperitoneally induced convulsions in three of the four mice treated. No convulsions occurred when sodium orthophosphate was administered, indicating that the orthophosphoric radical, by itself, has no convulsive action, whereas, the orthophosphate of thiamine has such an action.

The authors then tested these substances on clinical and experimental diabetes mellitus; results were promising. Subcutaneous and oral administration of thiamine pyrophosphate to rabbits caused a decided fall in blood sugar levels, while in human cases of diabetes mellitus the oral administration of thiamine pyrophosphate and thiamine orthophosphate caused a reduction of blood sugar values and a disappearance of glycosuria. Six patients, to whom different doses of phosphoric esters of thiamine were administered, were observed. Sugar levels in the urine and in the blood were determined during the first three hours or during the first 24 hours following administration of the esters. The results were similar: diminution of sugar in the blood and disappearance of sugar from the urine one hour after administration. These experiments seem to indicate that the phosphoric esters of thiamine have a favorable action on carbohydrate metabolism. The action of the phosphoric esters seem to be similar to that of insulin. It is possible that these compounds can replace insulin and that insulin acts through the phosphorization of the thiamine. This interpretation would agree with Houssay's observation that the phosphate levels in the blood plasma fall through the action of insulin. R. Boulin, P. Uhry and co-workers have shown that during the diabetic coma the most important disturbance of carbohydrate metabolism is the increased pyruvic acid level in the blood, on which insulin has no effect. These authors used cocarboxylase and reported good results in 10 cases of diabetic coma. The results of Montes and Cárdenas, regulation of blood sugar by oral administration of cocarboxylase, and those of Boulin and Uhry, diminution of pyruvemia with intravenously administered cocarboxylase, prove the efficacy of this compound in the treatment of diabetes.

Bureau of Medical Economic Research

MATERNAL MORTALITY IN THE UNITED STATES IN 1949

FRANK G. DICKINSON, Ph.D.
and
EVERETT L. WELKER, Ph.D.
Chicago

The downward trend of maternal mortality in the United States continued through 1949, according to data collected from the state health departments. Provisional reports received in correspondence with the states furnished information on the numbers of live births and maternal deaths for 47 states and the District of Columbia. With the 1948 data for the nonreporting state, Rhode Island, an estimated maternal mortality rate of slightly less than one maternal death per 1,000 live births was obtained for the United States in 1949. The maternal mortality problem in the United States is no longer a serious national problem but is, rather, one for local action in those areas in which maternal mortality rates are still relatively high. The rate for the United States has been declining rather steadily since 1933, the first year in which all the states were in the birth and death registration areas. The rate for 1933 was 6.2 and the rates for the intervening years were as follows:

1934.....5.9	1939.....4.0	1944.....2.3
1935.....5.8	1940.....3.8	1945.....2.1
1936.....5.7	1941.....3.2	1946.....1.6
1937.....4.9	1942.....2.6	1947.....1.3
1938.....4.4	1943.....2.5	1948.....1.2

In 1933 the rate for all deaths in Sweden was 3.1 and for white deaths only in New Zealand, 4.4. When the 1949 rates are published for Sweden and New Zealand they, also, will probably be slightly below the provisional rate of one for the United States. Hence it should be clear to the public that the United States, with its variations in climate and population and with its extreme size, has just about caught up with these two small healthy countries with homogeneous populations. In fact, differences in future maternal mortality rates between these three and others of the healthier nations are likely to be so small in magnitude that they could be a result of minor errors in reporting births and deaths and in erroneously attributing some deaths of women (that is, in coding) to maternal causes.[1] In at least three ways 1949, therefore, marks an end of an era in maternal mortality: The United States is the first large nation to push its maternal mortality rate slightly below the apparently irreducible minimum of one maternal death per 1,000 live births; critics of the quality and quantity of medical care in America will probably no longer attempt to make unfavorable comparisons between the United States and any nation, large or small, in the matter of maternal mortality rates, and 1949 was a transition year in coding the causes of death, a transition from the fifth to the sixth revision of the International List.

FIFTH AND SIXTH REVISIONS OF THE LIST

In this study an attempt has been made to estimate the number of maternal deaths during 1949 on the basis of both the fifth and the sixth revisions of the International List in order to provide 1949 rates comparable to the maternal mortality rates for the preceding 10 years and to the rates of future years; our major interest is in comparisons with the 10 preceding years. The sixth revision of the International List went into effect in some states on Jan. 1, 1949. Of the 49 states, including the District of Columbia as a state for this purpose, only 23 states reported 1949 maternal deaths on the basis of both the fifth and sixth revisions of the list. Only in the United States was the sixth revision widely used before Jan. 1, 1950, the "effective" date for most of the other nations. Thus 1949 was a year of transition in coding the causes of death.

As might be expected, there is some difference of opinion as to the precise effect of the new list on the number of maternal deaths, but there is general agreement that the number of maternal deaths will be fewer.[2] Much will depend on the care taken by the physician when specifying the underlying cause of death on the new death certificate form. The present problem is to estimate the probable effect and to express it as a percentage of the fifth to the sixth and vice versa. Table 1 presents the number of maternal deaths in the 23 states where the coding was done under both the fifth and sixth revisions. The total number of maternal deaths in these 23 states for 1949 coded under the fifth revision was 1,316; the number under the sixth revision was 1,244; thus the latter was 94.5 per cent of the former and the former 105.8 of the latter (bottom row, table 1). On the basis of this information for these 23 states, we concluded for the purposes of this paper that for every 100 maternal deaths in 1949 coded under the sixth revision there would have been approximately 106 deaths under the fifth revision and for every 100 maternal deaths under the fifth revision there would have been approximately 95 deaths under the sixth revision.[3] Consequently, we shall call 106 and 95 per cent our comparability ratios, with the understanding that they are not based on maternal deaths in all states in 1949. The maternal mortality rates for the United States in 1949, 1.0 (0.98) based on the fifth revision of the International List and 0.9 (0.93) based on the sixth revision, must be considered provisional or estimated rates.[4] The "true" national rate for 1949 on the basis of either the fifth or sixth revision may never be known. (The rate for the 45 states which reported the number of maternal deaths under the sixth revision was 0.93.)

Director (Dr. Dickinson) and Associate in Mathematics (Dr. Welker), Bureau of Medical Economic Research, American Medical Association.

Virginia Van Heule Horan and Helen Hulings Boyles, research assistants in the Bureau of Medical Economic Research, prepared the tables.

1. The latest available published rates for the nations with the lowest maternal mortality rates are as follows: Australia (excluding aboriginals) 1947, 1.9; Canada 1948, 1.5; Denmark 1948, 0.9; England and Wales 1947, 1.2; Finland 1947, 2.1; Netherlands 1947, 1.4; New Zealand (excluding Maoris) 1947, 1.1; Norway 1947, 1.5; South Africa (rate per 1,000 [total] births for Europeans only) 1947, 1.4; Sweden 1945, 1.3, and Switzerland 1947, 1.8.

2. Erhardt, C. L., and Weiner, L.: Changes in Mortality Statistics Through the Use of the New International Statistical Classification, Am. J. Pub. Health. **40**:16 (Jan.) 1950.

3. Computation of the standard deviation for either of these two national comparability ratios, 1.06 and 0.95, would be misleading because the maternal deaths used in computing these ratios are not a random sample of the universe. Hence the reliability of each of these two ratios cannot be tested statistically. If these 23 state ratios (fifth to sixth revisions) were arrayed in descending order, it would be evident that the highest values are for the states with the largest number of maternal deaths. The ratios are greater than 1.08 for Georgia, Illinois, New York and North Carolina. On the other hand, the ratio is relatively low in all the states reporting fewer than 50 maternal deaths. The median, mode and mean of these 23 state ratios are 1.000, 1.000 and 1.016. Although a difference in this direction might be rationalized, the difference seems to be too great to result from purely random factors. Would the national ratio be 1.07 if Pennsylvania and Ohio, each with more than 100 maternal deaths, had coded their maternal deaths on the basis of both revisions? Since our sample includes fewer than one-half the maternal deaths in 1949, our comparability ratio must be used cautiously by statisticians. We have, therefore, deliberately rounded it to 1.06 as a warning to readers that they should await the findings of the National Office of Vital Statistics, which will code from the death certificates all maternal deaths on the basis of both the fifth and sixth revisions. Some authorities predict that this comparability ratio may be as high as 1.10. All we can say is that on the basis of our (biased) sample it is 1.058, which we have rounded to 1.06; conversely, we have rounded the ratio of the sixth to the fifth revision data from our computed national ratio of 0.9453 to 0.95. These two rounded values have been used in preparing the estimated rates—three in column 4 and 22 in column 5 of table 2 for those states which did not code on the basis of both the fifth and the sixth revisions.

4. The maternal mortality rate overestimates the true risk of death from these causes because the rate is based on registered births. If, in a given year, the estimated number of unregistered births is 5 per cent of the registered births the "correct" maternal mortality rate is the rate based on registered deaths divided by 1.05. While it is necessary in historical comparisons to use the traditional maternal mortality rate, the probability of surviving pregnancy, childbirth and the puerperium in any one year—say the current year—should be based on all live births, not merely on registered births. For a discussion of the tendency of the maternal mortality rate to overestimate the true risk of death from maternal causes see pages 48-49 of Vital Statistics Rates in the United States, 1900-1940, Bureau of Census, United States Department of Commerce, Government Printing Office, Washington, 1943. An unpublished report of a sample developed by the National Office of Vital Statistics in the process of coding the causes of all deaths in 1949 provides an entirely different reason for our believing that our estimated national maternal mortality rate of 0.98 is too high.

But the rates for all states in 1950 will presumably be based on the sixth revision. Hence the 1949 rates estimated on the basis of the fifth revision are more useful in making comparisons with rates for earlier years, and those based on the sixth revision, with 1950 and future years.

Table 2 presents the basic data on live births and maternal deaths in each state and in the United States for 1949 as well as the maternal mortality rates for 1949, 1948 and 1933. The reported number of maternal deaths coded under the fifth revision (column 3) and under the sixth revision (column 2) are presented; likewise the reported or estimated (by the comparability ratio) maternal mortality rates under the fifth and sixth revisions are shown in columns 5 and 4. No reference will be made hereafter in this paper to rates based on the sixth revision.

RATES AND RANGE DECLINE

In the comparison of the state rates in column 5 (fifth revision) for 1949 with those for 1948 in column 6, declines are indicated for 35 states, including the District of Columbia. For five states the rates were unchanged and for only 9 were there

TABLE 1.—*Comparability Ratios for Twenty-Three States*

State	Number of Maternal Deaths: 5th Revision (1)	Number of Maternal Deaths: 6th Revision (2)	Ratio 5th to 6th (3)
Delaware	5	5	1.000
District of Columbia	15	17	0.882
Georgia	185	171	1.082
Illinois	144	129	1.116
Iowa	35	36	0.972
Kansas	25	27	0.926
Kentucky	99	94	1.053
Maryland	35	36	0.972
Montana	15	15	1.000
Nebraska	24	25	0.960
Nevada	4	4	1.000
New Hampshire	8	8	1.000
New York	238	218	1.092
North Carolina	142	128	1.109
North Dakota	9	9	1.000
Oklahoma	71	69	1.029
Oregon	21	20	1.050
Utah	10	10	1.000
Vermont	4	4	1.000
Virginia	88	84	1.048
Washington	36	36	1.000
West Virginia	53	52	1.019
Wisconsin	49	47	1.064
Totals	1,316	1,244	.....
Ratio of totals	.....	.....	1.058

increases from 1948 to 1949. Most of these increases were very slight. Many of the individual states have rates which are truly astounding.

Our present national rate of 1.0 for 1949 compares favorably with the 0.9 reported for Denmark for 1948, the lowest ever recorded by any nation in published reports now available. In the United States there were 26 states with rates lower than this record of 0.9. It has been previously pointed out in many articles that international comparisons between the United States and the small countries with homogeneous populations are somewhat strained. In spite of the handicap placed on the United States by such comparisons, it is gratifying to see that these obstacles have been almost entirely overcome in the problem of maternal mortality and that we are now apparently almost tied with the leader. It is even more startling that 30 states, more than one half of the total, have rates actually lower than 1.0. It should also be noted that these low rates are not chance occurrences for 1949 only, because many of these states have been consistently better than any nation in the world. In many instances the populations of the states in question are larger and less homogeneous than those of the small nations with the outstanding health records frequently cited in the literature.

Even in the 17 states with rates over 1.0, childbearing is becoming quite safe. Only two states have rates above 2.0; Mississippi has a rate of 2.4 and Alabama, a rate of 2.1. There are 14 states with rates within the range 1.1 to 1.9 inclusive.

TABLE 2.—*Maternal Mortality in the United States and Each State, 1933, 1948 and 1949* *

	Live Births (1)	1949 Maternal Deaths Reported: 6th Rev. (2)	1949 Maternal Deaths Reported: 5th Rev. (3)	Deaths per 1,000 Live Births, 1949: 6th Rev.† (4)	Deaths per 1,000 Live Births, 1949: 5th Rev.‡ (5)	1948 (6)	1933 (7)
Alabama	83,222	161	..	1.9	2.1	2.3	7.5
Arizona	19,714	27	..	1.4	1.5	1.3	6.5
Arkansas	47,700	81	..	1.7	1.8	2.1	7.8
California	240,504	163	..	0.7	0.7	0.9	4.6
Colorado	32,345	29	..	0.9	0.9	1.0	6.2
Connecticut	30,861	25	..	0.6	0.7	0.6	5.0
Delaware	7,546	5	5	0.7	0.7	1.1	6.9
District of Columbia	27,061	17	15	0.6	0.5	0.9	5.0
Florida	61,833	108	..	1.7	1.9	1.9	11.5
Georgia	93,557	171	185	1.8	2.0	2.1	7.5
Idaho	15,802	14	..	0.9	0.9	0.8	4.3
Illinois	185,593	129	144	0.7	0.8	0.8	5.0
Indiana	93,949	62	..	0.7	0.7	1.0	5.9
Iowa	61,765	36	35	0.6	0.6	0.8	5.3
Kansas	42,514	27	25	0.6	0.6	0.8	5.5
Kentucky	75,610	94	99	1.2	1.3	1.5	5.3
Louisiana	74,935	94	..	1.3	1.3	1.7	8.4
Maine	21,941	18	..	0.8	0.9	0.8	7.0
Maryland	54,048	36	35	0.7	0.6	0.9	5.0
Massachusetts	96,041	58	..	0.6	0.6	0.7	6.7
Michigan	156,469	...	105	0.6	0.7	0.8	6.1
Minnesota	74,036	...	54	0.7	0.7	0.7	4.4
Mississippi	66,128	147	..	2.2	2.4	2.6	7.3
Missouri	87,039	72	..	0.8	0.9	1.1	5.8
Montana	15,359	15	15	1.0	1.0	0.9	5.7
Nebraska	31,482	25	24	0.8	0.8	0.7	4.6
Nevada	3,737	4	4	1.1	1.1	1.6	8.1
New Hampshire	12,228	8	8	0.7	0.7	1.2	6.9
New Jersey	97,414	72	..	0.7	0.8	0.8	5.4
New Mexico	20,326	29	..	1.4	1.5	2.4	8.6
New York	302,730	218	238	0.7	0.8	0.9	6.2
North Carolina	107,150	128	142	1.2	1.3	1.9	6.8
North Dakota	16,836	9	9	0.5	0.5	1.0	4.9
Ohio	183,838	108	..	0.6	0.6	0.9	6.1
Oklahoma	49,971	69	71	1.4	1.4	1.1	6.5
Oregon	35,062	20	21	0.6	0.6	0.4	5.5
Pennsylvania	224,510	149	..	0.7	0.7	1.0	5.8
Rhode Island	16,861	22§	22§	1.3	1.3	1.3	5.7
South Carolina	58,486	...	104	1.7	1.8	2.4	8.0
South Dakota	17,382	10	..	0.6	0.6	1.0	4.8
Tennessee	82,307	110	..	1.3	1.4	1.8	6.0
Texas	202,094	235	..	1.2	1.2	1.5	7.7
Utah	21,202	10	10	0.5	0.5	0.6	4.5
Vermont	9,051	4	4	0.4	0.4	1.0	5.7
Virginia	82,761	84	88	1.0	1.1	1.4	6.3
Washington	55,368	36	36	0.7	0.7	0.5	6.4
West Virginia	52,370	52	53	1.0	1.0	1.1	5.7
Wisconsin	82,736	47	50	0.6	0.6	1.1	5.0
Wyoming	7,359	3	..	0.4	0.4	1.1	5.7
UNITED STATES	3,558,551	3,291	3,482	0.93	0.98	1.2	6.2

* Source: 1949 provisional data collected in correspondence with state health departments. Vital Statistics of the United States, 1948, Part II, National Office of Vital Statistics, Public Health Service, Federal Security Agency, Washington, 1950, pp. 94, 508. Vital Statistics Rates in the United States, 1900-1940, Bureau of the Census, U. S. Department of Commerce, Washington, 1940, p. 62).

† Rates in column 4 estimated by comparability ratio (0.95) for states not coding (..) deaths on sixth revision (column 2).

‡ Rates in column 5 estimated by comparability ratio (1.06) for states not coding (..) deaths on fifth revision (column 3).

§ 1948 data.

A large majority of these 14 states have shown a decline from 1948 to 1949 in maternal mortality rates. Even the highest state rate for 1949 of 2.4 was about one-half the lowest state rate in 1933, a rate of 4.3 maternal deaths per 1,000 live births.

As the rates decline, uniformity in state rates is being approached more rapidly than might be expected. In 1933 the range from the lowest to the highest state rate was 7.2 maternal deaths per 1,000 live births, while in 1949 the range had been reduced to 2.0, a decline of 72 per cent. The present low national rate has been achieved by reductions in all the states and not just by reductions in the more favored states. It has been the result of the efforts in every section of the nation to reduce the number of maternal deaths from each cause.

UNSTABLE RATES

From the statistical viewpoint, the small number of maternal deaths in some states has created a new problem in analyzing state maternal mortality rates. Only four maternal deaths occurred in Nevada and in Vermont in 1949. One maternal death, more or less, in these states would have resulted in a 25 per cent change in the maternal mortality rate. The situation was even more unstable in the state of Wyoming, where only three maternal deaths occurred. One can reduce this instability of maternal mortality rates for some of the states by considering three year averages centered on the middle year. Presumably the three year average for 1950-1952 will be for the first future trio of years which would not involve the coding difficulties; that is, the sixth revision would be used in all three years.

TABLE 3.—*Regional Maternal Mortality Rates in the United States, 1949 (Deaths per 1,000 Live Births)**

Division †	Rate ‡
United States	1.0
New England	0.7
Middle Atlantic	0.8
East North Central	0.7
West North Central	0.7
South Atlantic	1.4
East South Central	1.8
West South Central	1.3
Mountain	1.0
Pacific	0.7

* Source: See table 2.

† New England (Maine, New Hampshire, Vermont, Massachusetts, Rhode Island, Connecticut). Middle Atlantic (New York, New Jersey, Pennsylvania). East North Central (Ohio, Indiana, Illinois, Michigan, Wisconsin). West North Central (Minnesota, Iowa, Missouri, North Dakota, South Dakota, Nebraska, Kansas). South Atlantic (Delaware, Maryland, District of Columbia, Virginia, West Virginia, North Carolina, South Carolina, Georgia, Florida). East South Central (Kentucky, Tennessee, Alabama, Mississippi). West South Central (Arkansas, Louisiana, Oklahoma, Texas). Mountain (Montana, Idaho, Wyoming, Colorado, New Mexico, Arizona, Utah, Nevada). Pacific (Washington, Oregon, California).

‡ Based on fifth revision.

Another method would be the grouping of states into divisions such as the nine census divisions as shown in table 3. The highest rate, 1.8, occurs in the East South Central division; four divisions are tied at the lowest rate, 0.7. These rates indicate that the major problem in maternal mortality occurs in the South. The racial composition in the southern states may explain some of the excess of their rates above those of the other divisions. The major disadvantage in the use of nine divisions lies in the fact that maternal mortality should now be considered primarily a local problem and the health leaders in individual states (and large cities) will still be interested in comparisons between states rather than between groups of states. It should be noted that apparently no nation in the world has yet achieved a maternal mortality rate as low as 0.7, the rate for four divisions.

The maternal mortality rate is a crude rate rather than an age-specific rate. The rate, however, is closely associated with the age of the mother. Table 4 shows the age distributions of maternal deaths in 1933 and 1948 together with the age-specific maternal mortality rates. Table 5 shows the number and percentage distributions of all live births by the age of the mother. The safest childbearing age is still between 20 and 29 years. The age-specific mortality rates for the two age groups in this range differed much more in 1933 than they did in 1948. In 1933 the maternal mortality rate in the age group 20 to 24 years was 4.3 maternal deaths per 1,000 live births, 0.8 below the 5.1 rate for the age group 25 to 29 years; in 1948 these two rates were 0.7 and 0.9, respectively, a difference of only 0.2. The rates differed so greatly in 1933 that it is possible to say that only in the age group 20 to 24 years was the risk of maternal death relatively low. This age range in 1948 can be extended to include ages 20 to 29, or even ages 15 to 29. In 1948 a sharp difference in the risk of maternal death occurred beyond the age of 30. In 1933 the situation was somewhat different, with relatively high age-specific rates, even in the lower age brackets, and no sharp break occurring between age groups except above the age group 40 to 44. It seems obvious from the age-specific rates that the decided reduction in maternal mortality has been well distributed throughout the entire range of ages. The medical profession would like to make childbearing safer at all ages, but for the older mothers and for those under age 15 the problem will continue to be rather difficult.

TABLE 4.—*Maternal Deaths and Mortality Rates by Age of Mother in the United States, 1933, 1948 (Deaths per 1,000 Live Births)**

Age of Mother (in Years)	1933 Number (1)	1933 Rate (2)	1948 Number (3)	1948 Rate (4)	Decrease in Rate (5)
10-14	87	12.8	18	3.7	72%
15-19	1,441	5.7	435	1.0	82
20-24	2,646	4.3	884	0.7	83
25-29	2,753	5.1	860	0.9	83
30-34	2,578	7.3	844	1.5	80
35-39	2,324	10.6	772	2.7	75
40-44	932	12.5	316	4.2	66
45-49	182	17.8	31	6.1	66
50-54	3	24.6	2	12.3	50
Total †	12,885	6.2	4,122	1.2	81

* Source: Mortality Statistics, 1933, Bureau of the Census, U. S. Department of Commerce, Washington, 1936, p. 140. Vital Statistics of the United States, 1948, Part I, National Office of Vital Statistics, Public Health Service, Federal Security Agency, Washington, 1950, p. 156.

† Ages not stated included in total.

TABLE 5.—*Number of Live Births and Percentage of Total Live Births by Age of Mother in the United States, 1933, 1948**

Age of Mother (in Years)	1933 Number (1)	1933 Percentage (2)	1948 Number (3)	1948 Percentage (4)
Under 15	2,084	0.1	4,884	0.1
15-19	251,131	12.1	431,933	12.2
20-24	620,418	29.8	1,159,877	32.8
25-29	539,606	25.9	980,904	27.8
30-34	353,495	17.0	580,481	16.4
35-39	218,411	10.5	289,421	8.2
40-44	76,361	3.7	74,764	2.1
45-49	7,400	0.3	5,053	0.2
50 and over	122	0.0	102	0.0
Not stated	11,704	0.6	7,589	0.2
Total	2,081,232	100.0	3,535,008	100.0
Average age of mother	27.3 yr.		26.6 yr.	
Median age of mother	26.5		25.9	

* Source: Birth, Stillbirth, and Infant Mortality Statistics, 1933, Bureau of the Census, U. S. Department of Commerce, Washington, 1936, p. 111. Vital Statistics of the United States, 1948, Part II, National Office of Vital Statistics, Public Health Service, Federal Security Agency, Washington, 1950, p. 100.

The age of mothers has declined slightly between 1933 and 1948. (The total numbers of live births were 2,080,000 in 1933 and 3,535,000 in 1948.) If one considers only live births, in 1933 the mother's average (mean) age was 27.3 years; in 1948 the average was only 26.6 years. The median ages were 26.5 years and 25.9 years, respectively. The percentage distributions are shown in table 5. The most notable changes occurred

in the age groups 20 to 24 and 25 to 29. In 1948 each of these two groups was about two or three percentage points above the values recorded in 1933. Conversely, the percentage of mothers over the age of 34 decreased from 15.1 per cent in 1933 to 10.7 per cent in 1948, a decrease which partially explains the reduction in the maternal mortality rate. This age factor was probably more than counterbalanced by the increase in the percentage of first births from 31.7 per cent to 35.6 per cent. The tremendous reduction from 6.2 in 1933 to 1.2 in 1948 (in the crude rate) is, therefore, primarily due to the reduction in the age-specific rates and is only mildly influenced by the counterbalancing changes in age and first births. This is obvious if one notes that no age-specific mortality rate in 1933 was even close to the 1.2 recorded in 1948 for the entire United States. In fact, the risk of maternal death in the age group 45 to 49 in 1948 was less than in the age group 30 to 34 in 1933.

CAUSES IN 1933 AND 1948

Table 6 shows basic data for an analysis of maternal mortality by cause in 1933 and 1948. These two years were chosen because 1933 is the first year for which all the states were in both the death and birth registration area and 1948 was the last year for which data by cause are available; 1948 is also the last year for which the fifth revision of the International List was generally used. Deaths in 1933 were coded on the basis of the 1929 (the fourth) revision of the International List. Hence we found it necessary in preparing table 6 to make certain adjustments[5] to allow for the changes in coding which went into effect in 1939 with the fifth revision. Although the same groups of code numbers for maternal deaths, 140-150, were used in both the fourth and fifth revisions, there were differences in the exact types of causes encompassed by some of these 11 code numbers. This procedure required certain combinations of some of the code numbers (140-150) of the fifth revision in order to obtain comparable groupings of maternal deaths by cause in 1933 and 1948. The combinations of causes were made in terms of the fifth rather than the fourth revision (footnote to table 6).

Table 6 shows the number of maternal deaths, the maternal death rate and the percentage of deaths attributed to each of seven groups of causes for 1933 and 1948, together with the percentage decrease in rates from 1933 to 1948. The totals for all causes of maternal deaths are presented in row 1. The percentage of maternal deaths attributed to "abortion with mention of infection" (row 2) was 15.8 in 1933 and less than half that figure, 7.0, in 1948 (columns 3 and 6). "Abortion without mention of infection" (row 3) and "ectopic gestation" (row 4) were of nearly equal importance in both years. "Hemorrhage of pregnancy and of childbirth and puerperium" (row 5) increased in importance from 10.4 per cent in 1933 to 18.8 per cent in 1948. There was an increase of 3 per cent in "toxemias of pregnancy and puerperium" (row 6), the leading cause in 1948 and the second in 1933, between the two years. There was a decrease of 3 per cent in "other diseases and accidents of pregnancy; infection during childbirth and puerperium" (row 7), the leading cause in 1933 and the second in 1948. There was no change in "other accidents of childbirth; other and unspecified conditions of childbirth and puerperium" (row 8).

There was a decided decrease in the rates for each of the causes in the interval from 1933 to 1948. The percentage decreases (column 7) ranged from 66 for hemorrhage of pregnancy, childbirth and the puerperium (row 5) to 92 for abortion with mention of infection (row 2). This gives some support to the belief that the reduction in maternal deaths from hemorrhage is more difficult to achieve than reduction in maternal deaths from some of the other causes. Particularly striking is the reduction in the maternal mortality rate from abortion with mention of infection (row 2) from 0.98 (column 2) in 1933 to 0.08 (column 5) in 1948. The second largest percentage reduction in the rate was 84 for other diseases and accidents of pregnancy and infection during childbirth and the puerperium (row 7). Since accidents account for a small portion of the deaths from this group of causes, this decrease is primarily a decrease in deaths due to infections. These figures suggest that newer technics, more effective drugs and increased hospitalization are assisting in the reduction of maternal deaths due to infections.

TABLE 6.—*Number and Percentage of Total Maternal Deaths, Mortality Rates and Percentage Declines, by Cause; 1933 and 1948* *

Cause †	1933			1948			Percentage Decrease in Rates from 1933 to 1948
	Number of Deaths (1)	Deaths per 1,000 Live Births (2)	Percentage of Total (3)	Number of Deaths (4)	Deaths per 1,000 Live Births (5)	Percentage of Total (6)	(7)
1. Diseases of pregnancy, childbirth and the puerperium (140-150)	12,885	6.19	100.0	4,122	1.17	100.0	81
2. Abortion with mention of infection (140)	2,037	0.98	15.8	289	0.08	7.0	92
3. Abortion without mention of infection (141)	640	0.31	5.0	207	0.06	5.0	81
4. Ectopic gestation (142)	610	0.29	4.7	243	0.07	5.9	76
5. Hemorrhage of pregnancy and of childbirth and puerperium (143, 146)	1,339	0.64	10.4	773	0.22	18.8	66
6. Toxemias of pregnancy and puerperium (144, 148)	3,055	1.47	23.7	1,102	0.31	20.7	79
7. Other diseases and accidents of pregnancy; infection during childbirth and puerperium (145, 147)	3,409	1.64	20.5	964	0.27	23.4	84
8. Other accidents of childbirth; other and unspecified conditions of childbirth and puerperium (149, 150)	1,795	0.86	13.9	544	0.16	13.2	81

* Source: Mortality Statistics, 1933, Bureau of the Census, U. S. Department of Commerce, Washington, 1936, p. 140. Vital Statistics of the United States, 1948, Part I, National Office of Vital Statistics, Public Health Service, Federal Security Agency, Washington, 1950, p. 156.

† The code numbers in parentheses are from the Manual of the International List of Causes of Death, fifth revision, Bureau of the Census, U. S. Department of Commerce, Washington, 1940. The code numbers 143, 146 from the 1938 revision correspond with the code number 144 from the 1929 revision. The code numbers 144, 148 from the 1938 revision correspond with the code numbers 146, 147 from the 1929 revision. The code numbers 145, 147 from the 1938 revision correspond with the code numbers 143, 145, 148 from the 1929 revision.

Since neither of us is a physician, we asked two well qualified obstetricians to comment on table 6 for the purpose of presenting an informed medical opinion of the reasons for the sharp declines in the seven groups of causes of maternal mortality. These two physicians prefer to remain anonymous. Their statement follows:

"In reviewing table 6 from the viewpoint of possible factors which could account for the reduction in mortality between 1933 and 1948 from the seven groups of causes, it is possible to summarize the factors under three definite categories: (1) care, that is, improved medical care of pregnant women, particularly intranatal and postnatal care in hospitals, which involves better training on the part of physicians and some improvements in methods which have been devised since 1933; (2) antibiotics and blood, that is, the development of antibiotics and the greater availability and use of blood, blood substitutes and blood derivatives since 1933, and (3) earlier diagnosis, that is, provision for better prenatal care for a larger percentage of mothers than in 1933 making it possible to recognize unfavorable conditions in a higher percentage of pregnant women than in 1933.

5. Dunn, H. L., and Shackley, W.: Comparison of Cause-of-Death Assignments by the 1929 and 1938 Revisions of the International List: Deaths in the United States, 1940, Department of Commerce, Bureau of the Census, Vital Statistics-Special Reports **10**: 165 (June 14) 1944.

"We are listing below for each of the seven groups of causes in table 6 the one or more of these three factors primarily responsible for reductions in mortality and in the order of their importance.

Row 2 (140). Abortion with mention of infection: antibiotics and blood, plus care.
Row 3 (141). Abortion without mention of infection: care.
Row 4 (142). Ectopic gestation: early diagnosis; care (surgery); blood.
Row 5 (143, 146). Hemorrhage of pregnancy and of childbirth and puerperium: care; blood.
Row 6 (144, 148). Toxemias of pregnancy and puerperium: early diagnosis; care.
Row 7 (145, 147). Other diseases and accidents of pregnancy; infection during childbirth and puerperium: antibiotics; care.
Row 8 (149,150). Other accidents of childbirth; other and unspecified conditions of childbirth and puerperium: care.

"It will be noted that only the third factor, care, is given as a factor in the explanation of a sharp decline in maternal mortality from each of the seven groups of causes. Early diagnosis or prenatal care plays a significant role in ectopic gestation and toxemias of pregnancy and in assuring adequate size of the birth canal for safe delivery. Although educational programs for expectant mothers have doubtlessly been effective in reducing deaths from abortion with and without infection, the antibiotics and the availability of blood have been primarily responsible for the reduction in maternal deaths due to other diseases and accidents of pregnancy and infections during childbirth and the puerperium (row 7).

"It should also be noted that the two largest numbers of maternal deaths for 1933 and 1948 are found in rows 6 and 7. Ectopic gestation (row 4) and hemorrhage of pregnancy and of childbirth and puerperium (row 5) are the only causes of maternal deaths in 1948 which show a percentage decline in the rate (column 7) markedly less than the over-all decline of 81 per cent in the entire maternal mortality rate. It is in this area of the risk of childbearing that prenatal care may make its greatest contribution; but the physician will still play the primary role since it is only on his interpretation of findings that treatment will be given. If the patient will come early to the physician, ectopic gestation may be discovered early. If the patient is taught that any spotting or bleeding during pregnancy is potentially dangerous and that she should consult her physician at once, the mortality can be further reduced. If the patient is making the properly spaced visits to the physician so that a profile of her blood pressures, urine examinations and weight has accumulated on her chart, the physician can make the diagnosis of toxemia of pregnancy relatively early.

"In every one of these situations described by these seven groups of causes of maternal mortality, the physician is the key factor. The purpose of health education in all of its ramifications is, therefore, to get the patient to the physician early in pregnancy. In summary, this analysis of the reduction in the mortality rates by seven groups of causes indicates that the improved training and the increased skill of the physician are by far the most important factors."

The rates by cause for the nine geographic divisions are shown in table 7. (The difficulty faced in the compilation of table 6—translation of coding of the causes of death in the 1929 revision to the 1938 revision of the Manual of the International List of Causes of Death—does not arise in table 7, as the data are for 1948 only.) There is considerable variation in the rates by cause in the different divisions. The high maternal mortality rate for the East South Central division is apparently due to excessive numbers of deaths from toxemias of pregnancy (row 6) puerperal toxemias (row 10) hemorrhage of childbirth and the puerperium (row 8) and infection during childbirth and the puerperium (row 9). Physicians in the individual states are undoubtedly aware of the specific problems within their areas and continued reduction in these rates can be anticipated.

THE BASE—10,000 OR 1,000

Now that the maternal mortality rates for the 30 states and for the entire nation are less than one maternal death per thousand live births, there will undoubtedly be some tendency to make the rate base 10,000, even 100,000, live births instead of the traditional 1,000 live births. The rate based on 10,000 live births would be 10 instead of the 1.0 based on the traditional 1,000. The number of maternal deaths per 10,000 live (or total) births has rarely been used as the maternal mortality rate for a nation. Although the avoidance of decimals in rates may have some small merit, it seems to us that a change in the rate base from 1,000 to 10,000 live births would be unwarranted and would probably be misleading in any subsequent historical comparisons with earlier years. Revisions of the International List complicate historical comparisons; a change in the rate base would be another complication.

Since all maternal deaths are included in the number of maternal deaths whether the pregnancy was terminated by an abortion (miscarriage), a stillbirth or a live birth, there is, admittedly, some inconsistency in using only live births in the denominator. But it does not seem advisable at this time to add fetal deaths, which have been excluded heretofore, largely because of the lack of accurate and complete data.

In the whole range of vital statistics the maternal mortality rate is a peculiar rate. It is a crude rather than an age-specific rate. It has been customary to refer to the number of deaths —from all causes combined—per 1,000 persons at all ages as the crude death rate for the whole nation. The age distribution of mothers is limited and is not subject to such great changes as could and have occurred in the entire population. The maternal mortality rate is, therefore, not as "crude" as the crude death rate for the entire population. Expressing the maternal mortality rate as the number of deaths per 1,000

TABLE 7.—*Regional Maternal Mortality Rates in the United States by Cause, 1948 (Deaths per 1,000 Live Births)**

Cause †	United States (1)	New England (2)	Middle Atlantic (3)	East North Central (4)	West North Central (5)	South Atlantic (6)	East South Central (7)	West South Central (8)	Mountain (9)	Pacific (10)
1. Diseases of pregnancy, childbirth and the puerperium (140-150)	1.17	0.81	0.89	0.87	0.85	1.69	2.01	1.57	1.17	0.75
2. Abortion with mention of infection (140)	0.08	0.07	0.08	0.06	0.09	0.09	0.15	0.11	0.08	0.08
3. Abortion without mention of infection (141)	0.06	0.04	0.05	0.06	0.03	0.08	0.08	0.06	0.06	0.04
4. Ectopic gestation (142)	0.07	0.05	0.07	0.07	0.06	0.08	0.09	0.09	0.02	0.05
5. Hemorrhage of pregnancy (143) ‡	0.02	0.01	0.01	0.01	0.01	0.02	0.04	0.01	0.01	0.01
6. Toxemias of pregnancy (144) ‡	0.13	0.07	0.05	0.06	0.11	0.19	0.38	0.34	0.10	0.08
7. Other diseases and accidents of pregnancy (145) ‡	0.07	0.05	0.05	0.07	0.06	0.10	0.11	0.08	0.05	0.06
8. Hemorrhage of childbirth and the puerperium (146)	0.20	0.13	0.16	0.14	0.15	0.29	0.33	0.28	0.29	0.13
9. Infection during childbirth and the puerperium (147)	0.20	0.17	0.19	0.16	0.14	0.27	0.32	0.21	0.25	0.11
10. Puerperal toxemias (148)	0.18	0.11	0.11	0.11	0.12	0.35	0.35	0.22	0.16	0.11
11. Other accidents and specified conditions of childbirth (149)	0.09	0.05	0.09	0.09	0.04	0.10	0.11	0.08	0.09	0.09
12. Other and unspecified conditions of childbirth and the puerperium (150)	0.07	0.03	0.04	0.03	0.04	0.13	0.16	0.09	0.07	0.04

* Source: See table 6.
† The code numbers in parentheses are from the Manual of the International List of Causes of Death, fifth revision, Bureau of the Census, U. S. Department of Commerce, Washington, 1940.
‡ Death before delivery.

live births has, therefore, been consistent with the practice in regard to the crude death rate for the entire population.

The universe for maternal deaths is not the entire population but the number of women who are delivered during the course of the calendar year. It is customary to use 100,000 persons as the rate base in the computation of the mortality rate from a single cause or a group of causes—pneumonia or heart diseases. But this number of persons, the exposure group, would have no particular bearing on the problem of measuring maternal deaths (the puerperal rate). Even if the rate base were 100,000 females or 100,000 females at the childbearing ages, the resulting rate for a particular calendar year would be rather meaningless as a measure of probability. There would be, therefore, some slight precedent for using 100,000 live births in the computation of future national maternal mortality rates but little, if any, for using 10,000.

The disadvantage of making changes in the methods or data used in computing maternal mortality rates seem to outweigh the advantages, notably the elimination of the awkwardness of a second decimal place in the rate.

COMMENT

It must be remembered that maternal mortality rates are influenced by a variety of factors which vary from state to state. The inherent problems in certain areas of the United States are far more complicated than those in other areas. For this reason it is entirely possible that the records made by some of these states still having higher maternal mortality rates may represent an accomplishment in social progress even greater than that recorded by states reporting the lower maternal mortality figures. Nevertheless, we can see that local authorities, well able to analyze the situation in their own community, are presented with a tremendous opportunity for community service in those states where maternal mortality still maintains a relatively important position in the health picture.

SUMMARY

1. For the first time in history a large nation apparently had so few maternal deaths in relation to the number of live births in 1949 that the maternal mortality rate was below one.

2. In computing this estimate of the maternal mortality rate for the United States in 1949, it was estimated that the number of maternal deaths under the fifth revision of the International List was approximately 6 per cent greater than under the sixth revision.

3. A comparison of the maternal deaths by cause in 1933 and 1948 shows somewhat similar rates of decline except for hemorrhage of pregnancy, childbirth and the puerperium. The authors believe it would be inadvisable to shift from a base of 1,000 live births to a base of 10,000 live births in order to avoid decimal values now that the mortality rate has reached such low levels. Finally, it is good to know that the chances of an expectant mother surviving pregnancy, childbirth and the puerperium in the United States and in a few small countries are now 999 out of 1,000. The risk of dying in childbirth is now approximately one seventh of what it was a generation ago.

4. But we would be misinterpreting the nature of medical progress if, at this time, we did not call attention to the other side of the story. This triumphant conquest of the causes of maternal mortality will bring new challenges to future medical progress. It is to be earnestly hoped that when these mothers become, 20 to 50 years thereafter, potential candidates for the "older" causes of death that considerable gains will have been made in reducing the toll from these older causes. It is the disturbing premise of the practice of medicine that the physician cannot win. He can only raise the average age at death and increase the proportion of people who succumb to the older causes of death. But in providing more years of useful life to expectant mothers, the members of the medical profession and their auxiliary aids have contributed greatly to human and social progress in an era of wars and threats of war.

Medical Motion Pictures

A Place in the Sun. 16 mm., color, sound, showing time 25 minutes. Prepared by Peter Cohen, M.D., Supervisor, Cerebral Palsy Program for Northern California, University of California School of Medicine. Produced in 1950 by Jonathan Musser for the Junior League of San Francisco. Procurable on loan from the Junior League of San Francisco, Inc., Mark Hopkins Hotel, San Francisco.

This film depicts the cerebral palsy program in California. It shows the special examinations that are done in a cerebral palsy clinic to properly evaluate the child with cerebral palsy. It also goes on to show the various aspects of the program in a residence school for affected children, indicating the need for consideration of the whole child and the family. It demonstrates the activities in such a school, that is, physical, occupational and speech therapy, as well as the educational program. It also indicates how the program can be continued in the child's own community.

The presentation is free from unction and overacting. It shows follow-up and home care with the parents, to aid in the transition from the residential school to the home. The emphasis—an integrated one—on a combined therapy, including education and psychological evaluation, is especially good. Professional guidance is evident throughout, and the film gives evidence of authoritative, technical advice and emphasizes the importance of medical supervision.

Although this film will probably be most helpful in gaining the support of various lay groups for schools of the sort described, it has informative and inspirational value and could be shown profitably to almost any mature audience. The nonprofessional person will gain a real appreciation of the difficulties presented by these patients. Nurses, medical students and technicians will also be interested.

The narration is simple. There is no pretense of the film being a "high-pressured" production, but rather informative in a natural, easy manner. The photography is fair to good.

Diagnosis of Uterine Malignancies: 16 mm., sound, color, showing time 12 minutes. Prepared by Dr. Louis Schoffey, Dr. Theodore Eberhard and Dr. Warren Lang, Department of Obstetrics and Gynecology, Jefferson Medical College, Philadelphia. Produced in 1950 by the Jefferson Medical College through a grant for cancer teaching from the National Cancer Institute. Procurable on loan from the American Cancer Society or Jefferson Medical College, 1025 Walnut Street, Philadelphia 7.

The purpose of this motion picture, according to the authors, is to accent the importance of pelvic examination for the detection of pelvic cancer and to illustrate the proper technics, particularly those usable in the office of the physician. The important aspects and the special technical maneuvers for a pelvic examination are discussed and demonstrated by a physician doing a complete pelvic examination. The technic in taking a smear for a Papanicolaou study is then shown. The performance of a curettement of the uterine cavity and two circular biopsies of the cervix are also shown.

The value of rectal examination for determination of the extent of malignant infiltration, or detection of infiltration which might occur in the presence of a benign-looking external cervix, was left out entirely. Although the smear specimen for cytological examination was excellent, the discussion of the preparation was poor. The thinning out of the specimen and the fixation in alcohol and ether were not mentioned. The Papanicolaou smear procedure should precede the pelvic examination, as the use of lubricants in making this examination tends to wipe out the cancerous cells. The importance of endocervical curettage was entirely omitted. The importance of the finding of induration and friability of tissue, detected on palpation, and the use of a probe are also missing. Although the Schiller tincture test is included, the procedure and preparation are not carried out according to accepted technics. There should be included a reason for the performance of conization with a sharp scalpel in preference to diathermy. Induction and withdrawal of the tenaculum to avoid pinching and pulling constitute good advice.

If this film was better organized and more complete, it would have been a valuable aid in teaching general practitioners and medical students the importance of proper examination of the pelvis to detect early cancer. The photography is good; however the entire production is poorly organized.

Bureau of Legal Medicine and Legislation

MEDICOLEGAL ABSTRACTS

Powers of State Board of Health in Licensing Chiropractic Hospitals.—This was an action to review an order of the state board of health revoking the plaintiff's license to operate a chiropractic sanitarium. From a judgment in the trial court sustaining the board's action, the plaintiff appealed to the Supreme Court of Colorado.

In 1943 the state board of health issued to the plaintiff a temporary provisional license to operate a sanitarium with the following conditions: 1. Maternity cases shall not be received. 2. Surgery will not be performed. 3. Drugs or medicines shall not be administered. 4. No contagious or infectious cases will be admitted or treated. 5. The name "hospital" shall not be used in describing or designating the institution. In 1946, on notice and hearing, the defendant ordered and adjudged that this license be revoked. The present case is to review that order.

The court assumed at the outset that the scope of review was limited to the inquiry as to whether the board's jurisdiction has been exceeded, its discretion abused or its authority regularly pursued. The practice of chiropractic, said the court, is recognized and authorized by law. We must therefore accept such practice as a lawful occupation and as in the public interest. It may not be arbitrarily limited or discriminated against, and its advocates may lawfully erect and operate buildings and facilities for the treatment, according to its tenets, of patients seeking its aid, subject only to the limitations set out in the law and to reasonable regulations under the police power. Such regulations must, however, bear relation to the public health or welfare and must apply to all persons alike. The sole authority for the board in the issuance and revocation of licenses is contained in the state statute. This statute provides, so far as we are here concerned, that it shall be unlawful to open or maintain any hospital or other institution for the treatment or care of the sick or injured without first having obtained a license therefor from the state board of health; that the board "shall issue licenses to such applicants furnishing satisfactory evidence of fitness to conduct and maintain such institution in accordance with the provisions of this act and the rules and regulations adopted by such board; and such license shall be signed by the president and attested by the secretary of said board and have the seal there-of affixed thereto" and that licenses may be refused or revoked for failure to comply with the requirements of this act and of the rules and regulations of the board. This statute, said the Supreme Court, provides only for the issuance of permanent licenses, which shall continue until revoked.

It is at once apparent, said the Supreme Court, that the instrument issued to the plaintiff was in no respect a compliance with the statute under which the board must act. By its very terms it was not a license as authorized by the statute but an unauthorized, temporary provisional permit issued "pending consideration of an application for a permanent license." It was not signed by the president of the board nor even issued under its apparent authority, it was not attested by the secretary of the board, it did not bear its seal and most important of all it was not conditioned on a compliance with "the provisions of this act and the rules and regulations adopted by such board." Rather it was conditioned on five stated prohibitions no one of which was either a provision of the statute or properly or in fact a rule or regulation of the board. These prohibitions, the court continued, bear no relation to the sanitary conditions or the adequacy of equipment of the sanitarium, no relation to the training, competence or qualification of its personnel and no relation to the public health, morals, welfare or security. They are not set up as rules or standards for chiropractic sanitariums generally but are arbitrary and discriminatory restrictions against the applicant alone.

There is not a sentence in the issued license which follows the statute on which it is based. Instead of pursuing its statutory authority, the state board of health attempted to usurp the function of the legislature and set up a law of its own. However, the Supreme Court continued, the very fact that the board issued authority for the opening and operating of the sanitarium constitutes a finding of proper application for a license and satisfactory evidence of fitness to conduct and maintain the sanitarium. Such finding was a legal prerogative of the board and on such finding the board was legally obligated to issue a proper license in place of the one actually issued. Assuming that as done which should have been done, to wit the actual issuance of a proper license, and that such license was subject to revocation as provided by the statute, the revocation here ordered was of a certainty not in regular pursuit of authority. In the notice of hearing to revoke license upon which the hearing was based plaintiff was notified that the grounds of the revocation charged were that surgery had been performed, that drugs and medicines had been administered, that contagious and infectious diseases had been admitted and treated and that the name "hospital" had been used in describing or designating the institution. There was no charge that the licensee authorized or by negligence permitted surgery to be performed or drugs or medicine to be administered by persons or under conditions prohibited by law or regulation or that licensee violated any law or regulation in the admittance or segregation or treatment of contagious, infectious diseases or in the use of the word "hospital." The violation of void conditions could not justify revocation.

Accordingly, the Supreme Court held that the attempted revocation of license by the board was void and that the board should have issued a license in accordance with the law under which it acted. The judgment in favor of the board was therefore reversed.—*Spears Free Clinic & Hospital for Poor Children, Inc. v. State Board of Health, 220 P. (2d) 872 (Colo., 1950).*

Malpractice: Standards Applicable to Drugless Healers.—This was an action for damages alleged to have arisen out of the sanipractic treatment given to the plaintiff by the defendant. From a judgment in the trial court in favor of the defendant notwithstanding a verdict for the plaintiff, the plaintiff appealed to the Supreme Court of Washington.

The plaintiff had been informed by her physician that she had diabetes. She was averse to the administration of insulin, however, so she consulted the defendant, who informed her that by his method of treatment of diabetes neither insulin nor other drugs were used. There is evidence in the record from which the jury could have concluded that the plaintiff lost weight, had intermittent swelling of the ankles, a numbness of the limbs, impediment in vision and general physical weakness and had become irritable. After taking 41 treatments the plaintiff became alarmed, ceased taking them and entered a hospital. After a period of hospitalization and insulin therapy, the condition of the plaintiff improved to such an extent as to enable her to live a comparatively normal life.

We gather from the remarks of the trial judge, said the Supreme Court, that he considered a licensed sanipractor when operating within his school of treatment should be governed by the same rules applicable to a physician. The analogy does not apply to a drugless healer because he is restricted by statute to that which is permitted under the license issued to him. This is not a case where it can be said that the defendant was negligent in the performance of that which he undertook to accomplish. He knew the plaintiff had diabetes. It was not what he prescribed or instructed the plaintiff to do that created a foundation for legal liability. His fault, said the Supreme Court, lay in the fact that his method of treatment did not supply the pancreas deficiency necessary to retard the progress of the ailment with which the plaintiff was suffering. There was evidence before the jury sufficient to support a finding that the defendant knew or should have known, or discovered, that his method of treatment for diabetes was not of a character productive of reasonable success. When such a situation arises, concluded the Supreme Court, it then becomes the duty of a drugless healer to cease and desist from treating the patient and to advise the patient to seek other relief. Accordingly the judgment of the trial court in favor of the defendant was reversed and judgment in favor of the plaintiff was ordered.—*Carney et ux v. Lydon et ux, 220 P. (2d) 894 (Wash., 1950).*

CURRENT MEDICAL LITERATURE

AMERICAN

The Association library lends periodicals to members of the Association and to individual subscribers in Continental United States and Canada for a period of five days. Three journals may be borrowed at a time. Periodicals are available from 1939 to date. Requests for issues of earlier date cannot be filled. Requests should be accompanied with stamps to cover postage (6 cents if one and 18 cents if three periodicals are requested). Periodicals published by the American Medical Association are not available for lending but can be supplied on purchase order. Reprints as a rule are the property of authors and can be obtained for permanent possession only from them.

Titles marked with an asterisk (*) are abstracted below.

American Heart Journal, St. Louis

40:325-484 (Sept.) 1950

Myocardial Infarction Simulating Angina Pectoris. I. Stein.—p. 325.
*Myocarditis in Poliomyelitis. D. M. Spain, V. A. Bradess and V. Parsonnet.—p. 336.
*Active Rheumatic Carditis in Patients over 40 Years of Age. F. Wroblewski and W. J. Messinger.—p. 345.
Spontaneous Rupture of Papillary Muscle: Clinical Syndrome. H. Schwartz and F. R. Canelli.—p. 354.
*Air Travel and the Cardiac Patient: Analysis of Relevant Experimental and Empirical Data. S. H. May.—p. 363.
Effect of L-Nor-Epinephrine upon Corpuscular Volume and Hematocrit. G. C. Sutton, A. Kappert, A. Reale and others.—p. 369.
Action of Nor-Epinephrine and of Epinephrine on Ventricular Rate of Heart Block. M. H. Nathanson and H. Miller.—p. 374.
Prolonged Study of Oral Veratrum Viride in Treatment of Essential Hypertension. J. D. McNair, G. C. Griffith and S. R. Elek.—p. 382.
Abnormal Ballistocardiographic Patterns in Cardiovascular Disease as Recorded with Low-Frequency, Critically-Damped Ballistocardiograph. J. A. L. Mathers, J. L. Nickerson, T. C. Fleming and M. C. Patterson.—p. 390.
Experimental Cholesterol Arteriosclerosis: II. Changes Produced in Golden Hamsters and in Guinea Pigs. R. Altschul.—p. 401.
Electrokymographic Studies of Abnormal Left Ventricular Pulsations. J. B. Schwedel, P. Samet and H. Mednick.—p. 410.
Electrokymographic Studies of Relation Between Electrical and Mechanical Events of Cardiac Cycle in Wolff-Parkinson-White Syndrome. P. Samet, H. Mednick and J. B. Schwedel.—p. 430.
Prominent R Wave and Shallow S Wave in Lead V_1 as Result of Lateral Myocardial Infarction. L. Levy II, H. J. Jacobs, H. P. Chastant and H. B. Strauss.—p. 447.
Electrocardiographic Diagnosis of Combined Left and Right Ventricular Strain. R. H. Rosenman, S. Krause, W. Hwang and L. N. Katz.—p. 453.
Explanation of Wolff-Parkinson-White Syndrome. B. Kisch.—p. 466.

Myocarditis in Poliomyelitis.—Spain and his associates point out that little is known about the incidence and degree of involvement of the myocardium during poliomyelitis and that the clinical significance of this myocarditis is not too well established. They studied the hearts of 14 of 16 patients who died from poliomyelitis at Grasslands Hospital in Westchester County during 1947 to 1949, inclusive. Sections of myocardium were taken from all parts of the heart. Spinal cord and brain were examined in all cases. Microscopic changes of myocarditis were present in 12 of the 14 patients. The alterations varied considerably from one case to another and in the same case from section to section. The histological findings correlated closely with the duration of illness, but the severity of myocarditis could not be correlated with the clinical type of poliomyelitis. The heart in which there were obvious gross findings of myocardial involvement was that of the only patient who during life showed a possible sign of myocarditis. He had a rapid pulse, despite the fact that his temperature had dropped to near normal. The terminal episode was also suggestive of some degree of cardiac failure. The authors believe that myocarditis is etiologically related to the poliomyelitis group of viruses, because of the close correlation between the histological picture in the myocardium and the duration of illness and the presence of focal myocardial necrosis and nerve lesions in the myocardium. They cite other reasons for favoring the etiological role of the poliomyelitis virus but admit that the virus has never been isolated from the myocardium. They suggest that the myocardium be studied in experimentally produced poliomyelitis in monkeys and that isolation of the virus from the myocardium be tried.

Active Rheumatic Carditis in Patients over 40 Years of Age.—According to Wroblewski and Messinger, active rheumatic heart disease is generally unsuspected in patients over 40 years of age, unless the manifestations are classic. This disease was frequently seen in older patients at the hospital with which the authors are connected. These patients are, however, highly selected, since they were admitted only after protracted illness in general hospitals. The diagnosis of rheumatic heart disease had been made previously in only a few of these. The 34 cases with histological evidence of active rheumatic heart disease on which this report is based were selected from 1,930 autopsy protocols. The clinical records of these patients were studied to determine whether cardiac activity noted in the histological sections resulted in clinical manifestations and whether patients over 40 years of age who had postmortem histological evidence of rheumatic carditis, differed in clinical manifestations from patients in the younger age groups. The possibility of rheumatic heart disease was considered at one time or another during hospitalization in 12 of the 34 cases, while activity of the rheumatic process was suspected in seven of these 12 cases. Evidently, many of these clinical impressions were not sustained. A past history of rheumatic fever or rheumatic-like illness was obtained from 14 patients. The physical findings alone suggested heart disease in 27 cases. Of the 32 cases in which complete clinical data were available, 10 patients exhibited classic or obvious signs of clinical activity; 16 exhibited adequate signs, and in six, minimal or no manifestations were apparent. If the diagnosis of active rheumatic carditis had been considered seriously in spite of the age of the patient, a correct diagnosis could have been arrived at in most of them. Active rheumatic carditis should be considered more often in older patients. Unexplained fever and unusual responses to digitalis may be clues to such a diagnosis.

Air Travel and the Cardiac Patient.—According to May, there exist physiological, experimental and empirical data which suggest the existence of a factor in the human body which increases tolerance to oxygen want in the aged and in those with cardiac disease. It seems likely that the alerted adjustor mechanism of the carotid and the aortic nerve structures plays a greater role in the emergency of oxygen want. Some of the mechanisms which participate in the adjustment of the body to high altitude, besides the well known acclimatization by polycythemia to altitude, are, according to Wiggers, increased cardiac output and vital capacity, a slight shift of the p_H of the blood and an increased capacity of the blood to fix and use oxygen. There is also evidence that the coronary vessels dilate. The possibility of testing patients with cardiac disease under low oxygen pressures is regarded by the author as a strong argument for the high altitude tolerance of these patients. The collective experience of the airlines as well as the crucial experiment of the air evacuation of the sick and wounded from combat zones during the recent war seem to corroborate this view. The author presents three case histories to illustrate that patients with heart ailments tolerate air travel quite well and concludes that there is no valid objection to travel in modern air vehicles for patients with heart disease.

Am. Journal of Digestive Diseases, Fort Wayne, Ind.

17:293-322 (Sept.) 1950

Polyamine Formaldehyde Resin: IV. Clinical Evaluation in Treatment of Duodenal Ulcer. H. L. Segal, H. A. Friedman, E. E. Ellis and J. S. Watson Jr.—p. 293.
Noxious Antral Remnant in Treatment of Peptic Ulcer of Duodenum. F. G. Connell.—p. 296.
Induction of Normal Defecation Reflex by Distention of Rectal Stump Following Removal of Recto Sigmoid. I. H. Einsel and T. H. Einsel. —p. 298.
Effect of Cytochrome C and Sodium Succinate in Cases of Chronic Hepatic Disease. S. Zelman.—p. 300.
Takata-Ara Reaction in Differential Diagnosis and Prognosis of Jaundice. B. Shulman, F. Steigmann and E. W. Stevens.—p. 305.
Pseudoagglutinative Effect of Equine Gastric Mucin on Human Erythrocytes and Suggestive Evidence of Anti-Hr Component Therein. R. D. Barnard and R. G. Coren.—p. 311.
Fifteen Years' Study of Occult Lymphocytosis in 280 Hypercholesterolemia Patients. E. Tuttle.—p. 314.

American Journal of Tropical Medicine, Baltimore

30:599-802 (Sept.) 1950. **Partial Index**

Physiological Disposition of Diodoquin, Vioform, and Chiniofon in Rabbit as Determined with Radioiodine. W. T. Haskins, G. W. Luttermoser and F. J. Brady.—p. 599.
Effectiveness of Bismuthoxy *p*-N-Glycolylarsanilate (Milibis®) in Treatment of Intestinal Amebiasis. D. A. Berberian, E. W. Dennis and C. A. Pipkin.—p. 613.
Trial of Enteric-Coated Camoquin in Intestinal Amebiasis. M. T. Hoekenga and Q. Gonzalo Maximo.—p. 625.
Effect of Rice Powder on Growth of Cultures of Endamoeba Histolytica. C. L. Spingarn and M. H. Edelman.—p. 629.
Effect of X-Ray upon Growth and Infectivity of Endamoeba Histolytica. E. H. Sadun, J. N. Ané, F. W. Fuller and R. Lewis.—p. 635.
Simplified Casein Hydrolysate-Serum Medium for Cultivation of Trichomonas Vaginalis. J. J. Lash.—p. 641.
Laboratory Infection with Leishmania Donovani: Case Report. L. L. Terry, J. L. Lewis Jr. and S. M. Sessoms.—p. 643.
Observations on Recession of Malaria in Area of Southwestern Georgia. M. H. Goodwin Jr.—p. 651.
Heretofore Unreported Agglutinable Human Blood Factor and Its Possible Relationship to Blackwater Fever. D. C. A. Butts.—p. 663.
*Progress in Treatment of Trachoma with Chloromycetin (Chloramphenicol). M. J. Pijoan, E. H. Payne and J. Dineen.—p. 677.
Observations on Experimental Transmission of Japanese Encephalitis by Mosquitoes. H. S. Hurlbut and J. I. Thomas.—p. 683.
Japanese B Encephalitis: Complete Review of Experience on Okinawa 1945-1949. W. D. Tigertt, W. M. Hammon, T. O. Berge and others. —p. 689.
Geographical Distribution of Immunity to Yellow Fever Among Primates of Brazil. H. W. Kumm and H. W. Laemmert Jr.—p. 733.
Study of Concentration of Yellow Fever Virus which Will Infect Certain Species of Aedes Mosquitoes. H. W. Kumm and H. W. Laemmert Jr. —p. 749.
Diabetes Mellitus and Pylephlebitic Abscess of Liver Resulting from Schistosoma Mansoni Infestation. M. Seife and J. R. Lisa.—p. 769.
Seventeen Cases of Poisoning Due to Ingestion of Eel, Gymnothorax Flavimarginatus. C. T. Khlentzos.—p. 785.

Chloramphenicol in Treatment of Trachoma.—Pijoan and his co-workers report on cases of trachoma characterized by an acute onset of conjunctival inflammation, dense infiltration and papillary hypertrophy. In the early stages there existed in these patients a superficial inflammation of the cornea, particularly of the upper limbus region, some swelling of the lids and increased lacrimation. There was a follicular hypertrophy of the upper tarsal conjunctiva. Pannus was noted in all cases, and capillary loops were observed within the matrix of this structure. Corneal and conjunctival cicatrization was present in the later stages, and early deformities, such as cicatricial entropion were noted in some of the patients. Eight children and six adults were treated with chloramphenicol. The diagnosis was based on the slit lamp and biomicroscope examination, in addition to bacteriologic and physical examinations. Chloramphenicol was administered orally, 3 Gm. being given in divided doses at three-hour intervals for the first 24 hours, after which 250 mg. were given every three hours for at least four days. Most of the photophobia and lacrimation was materially reduced within 24 hours, and there was a reduction of approximately 85 per cent in opacities and inflammation within the next few days. The patients were hospitalized with bed rest in partly darkened rooms for four days and were on a regular diet. They were protected from dust and wind. Examination at the termination of treatment showed only one patient in whom further therapy appeared necessary. The authors feel that the benefits will probably be permanent, because there was no evidence of relapse over a period of three months.

Annals of Surgery, Philadelphia

132:161-320 (Aug.) 1950

*Cervical Arteriovenous Anastomosis in Treatment of Mental Retardation, Convulsive Disorders and Cerebral Spasticity. C. F. McKhann, W. D. Belnap and C. S. Beck.—p. 162.
Consideration of Bronchiogenic Carcinoma. E. A. Graham.—p. 176.
*Role of Adrenal Cortex in Postoperative Retention of Salt and Water. J. D. Hardy.—p. 189.
Complete Scalp Avulsion: Rational Treatment. Report of Cases: Experimental Basis for Production of Free, Hair Bearing Grafts from Avulsed Scalp Itself. M. P. Osborne.—p. 198.
Arterial Aneurysms. B. McSwain and W. Diveley.—p. 214.
Sterilization of the Intestinal Tract by Antibiotics and Supplemental Agents. E. J. Pulaski, J. F. Connell Jr. and S. F. Seeley.—p. 225.
Penicillin and Streptomycin in Treatment of Experimental Escherichia Coli Peritoneal Infection. H. W. Bloemers and J. E. Kempf.—p. 235.
Conservative Treatment of Salpingitis Complicating Myomata Uteri. H. C. Falk, C. Mandelbaum and G. Blinick.—p. 247.
Contribution to Surgical Significance of Aberrant Hepatic Ducts. V. Rapant and J. Hromada.—p. 253.
Thrombophlebitis Migrans: Case Report with Autopsy and Review of Literature. J. M. Sullivan and B. R. Walske.—p. 260.
Calcified Intracerebral Hematoma: Case Report and Review of Literature. F. W. Lusignan and G. O. Cross.—p. 268.
Tri-Locular Gastric Diverticulum Treated by Surgical Extirpation Through Thoraco-Abdominal Incision. M. L. Michel and W. T. Williams.—p. 273.
Perforation of Gallbladder into Free Peritoneal Cavity with Spontaneous Healing. V. Moragues and T. R. Simon.—p. 282.
Cystic Lymphangiomata of Greater Omentum. A. J. Beller and R. L. Nach.—p. 287.
Cholecysto-Choledochal Fistula: Unusual Form of Internal Biliary Fistula. A. Behrend and M. L. Cullen.—p. 297.
Plasmacytoma of Thyroid Gland. F. E. Barton and D. A. Farmer. —p. 304.
Catheterization of Portal Vein in Man Following Porto-Caval Anastomosis. C. T. Dotter, M. A. Payne and W. O'Sullivan.—p. 310.
Ainhum (Dactylolysis Spontanea): Review of 10 Cases. D. C. Hucherson.—p. 312.

Cervical Arteriovenous Anastomosis for Mental Retardation.—McKhann and his associates describe an operation to increase the arterial blood supply to the cortex of the cerebrum. This involves the production of an arteriovenous anastomosis between one of the carotid arteries and the internal jugular vein, with ligation of the jugular vein proximad to the anastomosis. It was thought that there might be in some conditions viable brain cells enmeshed in a gliotic process and that the function of these cells could be improved by increasing the blood supply to the brain. The operation was performed in 125 patients. Recently, the external carotid artery was used rather than the common carotid artery. The original common carotid-internal jugular anastomosis was done in 52 children and 26 adults, while the other patients were subjected to the later procedure. Children with developmental anomalies were excluded from this treatment, because it was reasoned that the operation could be successful only if there had been normal development with subsequent injury. Children with birth injury, birth anoxia, encephalitis, kernicterus, cortical atrophy secondary to subdural hemorrhage and lesions from meningitis and from hyperpyrexia were selected for treatment. The adults operated on had convulsive disorders secondary to organic change, idiopathic epilepsy, arteriosclerosis, cerebrovascular complications, sequelae of cerebral emboli and thrombosis not secondary to arteriosclerosis. It was found that the carotid-jugular anastomosis increases cerebral blood flow and that it may bring about a revascularization of the brain. Anastomosis between the external carotid artery and the internal jugular vein, within limits of a 3.5 to 4.0 mm. stoma, proved to be reasonably safe. About 35 per cent of the children and a small percentage of adults have shown postoperative benefit. The procedure is still in the trial stage and should be considered as representing a new approach to the problem rather than an aceptable and complete solution.

Adrenal Cortex and Postoperative Retention of Salt and Water.—Hardy points out that patients subjected to major surgical procedures frequently retain significant amounts of infused sodium chloride and glucose solutions during the immediate postoperative period. He felt that this retention of salt and water might be related to the activity of the adrenal cortex after the trauma of anesthesia and operation. In the absence of facilities for the fractionation of urinary corticoids, he selected the total eosinophil count as a measure of adrenocortical function. Infusions of 2,000 cc. of 5 per cent glucose in water and

of 1,000 cc. of 5 per cent glucose in 0.85 per cent sodium chloride solution were administered daily for three days following operation in five patients who had undergone partial colon resection, one a vagotomy and one a hemorrhoidectomy. The urinary volume and the total output (urine plus gastrointestinal suction) were correlated with the total eosinophil counts, and it was found that the curves could be almost superimposed. In a second group of three patients, one of whom underwent gastric resection, one resection of the right colon and one combined abdominoperineal resection, 750 cc. of a 5 per cent dextrose solution were administered in each of the first four six-hour periods postoperatively, and rates of urinary excretion of water, sodium, potassium and chloride were measured and correlated with the total eosinophil counts in each period. When adrenocortical function was maximal, as indicated by a profound fall in the total eosinophil count, there was a decreased rate of excretion of sodium, water and chloride, with an increased rate of excretion of potassium. The rates of excretion were identical with results obtained following the administration of desoxycorticosterone. The author discusses a number of factors which might affect the postoperative excretion of salt and water. The vigor of eosinophil response to trauma may be in some way related to the vitality of the patient. He draws attention to the diminished volume of fluids secreted into the intestinal tract during the first 24 hours postoperatively. This may represent another manifestation of a profound generalized derangement in the membrane permeability.

Blood, New York

5:793-886 (Sept.) 1950

*Hereditary Spherocytic Anemia in the Negro. C. E. Butterworth Jr., R. R. Kracke and W. H. Riser Jr.—p. 793.
Severe Mediterranean Anemia (Cooley's Anemia) in a Chinese Child. Q. B. DeMarsh.—p. 798.
Effect of Racial Mixtures upon Erythrocytic Sickling. J. H. Hodges. —p. 804.
Familial Nonspherocytic Hemolytic Anemia. E. Kaplan and W. W. Zuelzer.—p. 811.
*Paroxysmal Nocturnal Hemoglobinuria; Mechanism of Hemolysis and Its Relation to Coagulation Mechanism. W. H. Crosby and W. Dameshek. —p. 822.
Paroxysmal Nocturnal Hemoglobinuria; Specific Test for Disease Based on Ability of Thrombin to Activate the Hemolytic Factor. W. H. Crosby. —p. 843.
Microscopic and Histochemical Studies on Auer Bodies in Leukemic Cells. G. A. Ackerman.—p. 847.
Beta-Glucuronidase of Human White Blood Cells. R. J. Rossiter and E. Wong.—p. 864.
Efficiency of an Iron-Molybdenum Preparation as Evaluated by Means of Iron Absorption Tests. S. Gullberg and B. Vahlquist.—p. 871.
Cause of Sexual Differences in Erythrocyte, Hemoglobin and Serum Iron Levels in Human Adults. B. Vahlquist.—p. 874.

Hereditary Spherocytic Anemia in the Negro.—Butterworth and co-workers studied 12 persons representing four generations of a Negro family, two of whom, both women, appeared to have typical cases of hereditary spherocytic anemia. Splenectomy was performed on one. The blood values returned to normal, and the patient remained completely well. The second patient never had a hemolytic crisis, although reticulocytosis and the large size of the spleen indicated that the disease was active. Five persons were normal. The remaining five had microspherocytosis and an increased red cell fragility but were completely asymptomatic and appeared in good health. They were considered carriers of hereditary spherocytic anemia. This disease has always been thought to be transmitted as a simple mendelian dominant factor. With regard to the genetic mechanism involved, the presence of three recognizable categories—patients, carriers and normals—indicates at once that a simple single-gene, dominant-recessive relation is not the explanation. The suggestion is made that spherocytic anemia in the Negro is due to multiple factors. The high incidence of the disease in females is again pointed out.

Paroxysmal Nocturnal Hemoglobinuria.—Crosby and Dameshek studied the mechanics of hemolysis in the blood of six patients with paroxysmal nocturnal hemoglobinuria, a rare hemolytic anemia of obscure origin, characterized by a defect of the erythrocytes, which makes them susceptible to hemolysis by a normal plasma or serum factor. Results showed that the hemolytic reaction does not involve a complement-antibody reaction, but is rather an enzyme-like reaction that is related to the coagulation mechanism of the blood. Evidence suggests that the heat-labile hemolytic factor in paroxysmal nocturnal hemoglobinuria if not identical with the serum coagulation accelerator, resembles it in many aspects. The hemolytic factor is present in plasma as an inert precursor which is activated by thrombin. Bishydroxycoumarin (dicumarol®) inhibited hemolysis in a patient with paroxysmal nocturnal hemoglobinuria. Therapeutically, the drug was disappointing. It did not reduce the hemolytic precursor and did not prevent hemolytic crises, but its use was not dangerous, suggesting that it may be of value during crises of this disease when thrombosis threatens. Dilute heparin facilitated the activation of the hemolytic enzyme by thrombin. The use of heparin in paroxysmal nocturnal hemoglobinuria may be dangerous. Lysis of paroxysmal nocturnal hemoglobinuria of cells by a substance related to the clotting mechanism offers a new approach to the study of the coagulation problem.

Electroencephalography and Clin. Neurophys., Boston

2:243-372 (Aug.) 1950. **Partial Index**

Homeostasis of Cerebral Excitability. H. Davis.—p. 243.
Combined Photic and Metrazol Activation of Brain. H. Gastaut.—p. 249.
Experiences with Combined Stroboscopic and Metrazol Activation of EEG in Epileptics and in Patients Suspected of Having Seizures (Gastaut Technique). R. S. Schwab and J. A. Abbott.—p. 262.
Experimental Study of Mechanism of Photic Activation in Idiopathic Epilepsy. H. Gastaut and J. Hunter.—p. 263.
Electroencephalogram During Hyperventilation Followed by Apnoea: Preliminary Report. D. L. Lloyd-Smith.—p. 289.
Initial Survey of Slow Potential Changes Obtained Under Resting Conditions and Incident to Convulsive Therapy. S. Goldring, G. Ulett, J. O'Leary and A. Greditzer.—p. 297.
Studies of Regulatory Functions of Limbic Cortex. N. Sloan and H. Jasper.—p. 317.

Journal of Aviation Medicine, St. Paul

21:281-358 (Aug.) 1950

*Effect of Repeated Exposure of Human Subjects to 18,000 Feet Without Supplemental Oxygen, to Hyperventilation, and to 35,000 Feet with 100 Per Cent Oxygen for One Hour, on Ascorbic Acid Excretion and Plasma Level and on Urine pH. L. R. Krasno, J. H. Cilley, J. H. Boutwell and others.—p. 283.
*Cardiovascular Pressor Reflex Mechanism and Cerebral Circulation Under Negative G Head-to-Tail Acceleration. S. Rosenfeld and C. F. Lombard.—p. 293.
Extent of Pathological Damage to Animals Explosively Decompressed in Cold Environment. W. L. Burkhardt, R. E. Hedblom, A. W. Hetherington and H. F. Adler.—p. 304.
Medical Services of the Department of Defense. R. L. Meiling.—p. 309.
Performance Under Acute Hypoxic Stress in Acclimatized Mice. R. E. Wilhelm, M. S. Comess and J. P. Marbarger.—p. 313.
New Medical Service of the United States Air Force. H. G. Armstrong. —p. 318.
Early History of the Aero Medical Association. R. J. Benford.—p. 321.
Flight Training for Flight Surgeons. E. M. Wurzel.—p. 326.
Visibility of Cockpit Instruments. N. L. Barr.—p. 328.
Problems on Parachute Jumps Over the Andes. G. Garrido-Lecca Frias. —p. 343.

Hypoxia and Ascorbic Acid Excretion.—Krasno and his associates observed that exposure of human subjects to hypoxia in an altitude chamber appeared to alter the metabolism of ascorbic acid. They found that when subjects were receiving 91 mg. of ascorbic acid daily and were exposed to an altitude of 18,000 feet without oxygen supplementation, there occurred a gradual depletion of ascorbic acid. Evidence indicates that the depletion was due to increased utilization. When persons were receiving 141 mg. of ascorbic acid daily and were exposed three times a week to an altitude of 35,000 feet while breathing 100 per cent oxygen, a hyperexcretion of ascorbic acid occurred during four weeks of exposure. At this level of intake of ascorbic acid, it is unlikely that any tissue deficiency will occur with time. In view of the role that ascorbic acid plays in cellular oxidation-reduction reactions, its presence normally in a relatively high concentration in the adrenals and the observation that the vitamin may be depleted by repeated exposure to hypoxia, which also depletes body base, it is suggested that liberal quantities of fruit or fruit juices be supplied in the diet of persons who may be subjected to exposure to a discontinuous or continuous hypoxia, or to hyperventilation.

Effects of Acceleration.—Rosenfeld and Lombard are concerned with the effects of negative acceleration (negative gravity), by which they mean the acceleration that acts in the head-to-heart direction and that results in the force of inertia tending to throw the blood mass and organs toward the head. The study of comparative physiology reveals wide variations in

response of the various members of the mammalian family. The authors studied 28 animals, including 10 goats, 10 dogs, 5 monkeys and 3 rabbits. When the data obtained were compared with those available for man, it was found that the monkey and the dog respond in a manner that most closely parallels the reflex cardiovascular response shown by man during the action of negative gravity. It is believed that the animal or person experiences the most harmful insult to cerebral circulation at the termination of the acceleration. Factors that tend to maintain minute cardiac output, as well as factors preventing generalized vasodilatation, should be investigated for possibilities of offering greater tolerance to negative acceleration. It seems likely that the symptoms experienced by pilots exposed to negative gravity may be attributed to two phenomena: (1) the increase in intravascular and extravascular cephalic pressure and (2) the stagnation of cerebral flow. The former produces the feeling of extreme fulness of the head, while the latter is probably responsible for mental confusion, and loss of consciousness. The possibility of a central type of syncope from stimulation of the carotid sinus cannot be overlooked.

Journal of Bacteriology, Baltimore

60:215-368 (Sept.) 1950. **Partial Index**

Comparison of Phenylpyruvic Acid Reaction and Urease Test in Differentiation of Proteus from Other Enteric Organisms. S. D. Henriksen. —p. 225.
Sulfur Metabolism in Escherichia Coli: I. Sulfate Metabolism of Normal and Mutant Cells. D. B. Cowie, E. T. Bolton and M. K. Sands. —p. 233.
Rapid Assay for Growth: Determination of Microbiological Susceptibility and Fungistatic Activity. G. R. Mandels and R. G. H. Siu.—p. 249.
Effects of X-Rays Produced at 50 Kilovolts on Different Species of Bacteria. H. Fram, B. E. Proctor and C. G. Dunn.—p. 263.
Effect of Metabolites upon Growth and Variation of Brucella Abortus. R. J. Goodlow, L. A. Mika and W. Braun.—p. 291.
Nutrition and Role of Reducing Agents in Formation of Streptolysin O by Group A Hemolytic Streptococcus. H. D. Slade and G. A. Knox. —p. 301.
Nutritional Requirements for Hydrogenase Production by Escherichia Coli. D. Billen and H. C. Lichstein.—p. 311.
Morphological Characteristics of Paired Sulfonamide-Susceptible and Sulfonamide-Resistant Strains of Staphylococcus Aureus. M. E. Hunter, S. Mudd and M. A. Woodburn.—p. 315.
Studies on Metabolism of Blastomyces Dermatitidis. S. Levine and M. Novak.—p. 333.

Journal of Pediatrics, St. Louis

37:291-434 (Sept.) 1950

*Comparison of "Symptomatic Treatment," Gamma Globulin, and Penicillin in Treatment of Scarlet Fever. L. Weinstein and S. F. Potsubay.—p. 291.
*Aureomycin in Treatment of Pertussis: Preliminary Report. W. J. Miller and J. E. Ross.—p. 307.
Resuscitation of Newborn Infant: Use of Positive Pressure Oxygen-Air Lock. A. Bloxsom.—p. 311.
Incomplete Pancreatic Deficiency in Cystic Fibrosis of Pancreas. G. E. Gibbs, W. L. Bostick and P. M. Smith.—p. 320.
Cerebral Birth Injury in Retrospect. W. D. Belnap, C. F. McKhann and C. S. Beck.—p. 326.
Glycemic Response of Newborn Infant to Epinephrine Administration: Preliminary Report. M. M. Desmond, J. R. Hild and J. H. Gast. —p. 341.
Note on Treatment of Diaper Rash with Alkyl-Dimethyl-Benzyl-Ammonium Chlorides (Roccal). W. Pfeffer Jr. and C. A. Smith.—p. 351.
Measure of Immunologic Responses to Improved Preparation of Diphtheria and Tetanus Toxoids (Alum Precipitated) Combined with Pertussis Vaccine. R. M. Tyson, B. J. Houston and M. M. Paschkis. —p. 357.
Premature Mortality: Analysis of 518 Cases of Prematurity with Comparison of Negro and White Races. G. E. Brockway, E. T. Reilly and M. M. Rice.—p. 362.
Dehydrated Banana in Dietetic Management of Diarrheas of Infancy. J. H. Fries, N. J. Chiara and R. J. Waldron.—p. 367.
Purpura Following Exposure to DDT. F. E. Karpinski Jr.—p. 373.
High Gastrointestinal Obstruction in Newborn Infant: Radiological Interpretation. M. Dannenberg, C. Storch, S. D. Sternberg and C. Hoffman. —p. 380.

Treatment of Scarlet Fever.—Weinstein and Potsubay treated 255 patients with scarlet fever by three different regimens. The three types of treatment were a single intramuscular injection of 20 to 60 cc. of gamma globulin, penicillin in a dose of 15,000 units given intramuscularly every three hours (120,000 units daily) for 10 days and so-called symptomatic treatment, consisting of bed rest and throat irrigations. Gamma globulin was observed to cause rapid fading of the rash but had no effect on the streptococci in the pharynx, allowed the carrier state to persist as long as it did in untreated patients and had little, if any, effect on the development of suppurative complications or such nonsuppurative sequelae as rheumatic fever. Penicillin appeared to be the agent of choice in the treatment of scarlet fever, because it caused rapid disappearance of the local focus of infection, eradicated Streptococcus pyogenes from the pharynx speedily assured eradication of the carrier state and significantly decreased the incidence of serious suppurative complications. The problem of the occurrence of rheumatic fever and of glomerular nephritis following treatment of the initial streptococcic infection will be discussed in a later paper. In the group of patients given symptomatic treatment the course of the disease was more or less typical. There was a relatively slow recovery at the site of streptococcic invasion, frequent persistence of the organism for a period beyond the isolation time and the occurrence of local and distant bacterial and nonbacterial complications.

Aureomycin in Pertussis.—Miller and Ross treated with aureomycin six children with pertussis who were between the ages of 5 weeks and 3 years. Doses of 350 mg. per kilogram of body weight were given every 24 hours for periods of eight to 10 days. Hyperimmune serum was administered before the use of aureomycin in three cases, and, in one of these, streptomycin was given intramuscularly for an 18 hour period just preceding the start of aureomycin therapy. All the patients manifested severe types of the disease. Improvement in these patients after institution of aureomycin treatment was gradual and steady. Patients who were cyanotic and vomiting showed the greatest change. These manifestations usually cleared by the third to fifth day. Elevated temperatures, when present, subsided in this interval as well. Paroxysms of coughing persisted for a longer time but with steadily diminishing frequency. The patients were free of this symptom by the seventh to the tenth day after institution of the treatment. Convalescence after the initial period of improvement was uneventful. Despite poor prognosis, almost complete recovery occurred in less than two weeks in all the patients after the institution of aureomycin treatment. Although some of the patients received other therapy, the improvement in all occurred following aureomycin therapy alone. The uniformity of the recovery following aureomycin therapy is the best evidence for the effectiveness of the drug, although the small number of cases reported does not permit precise evaluation or adequate comparison with other methods of treatment.

Maine Medical Association Journal, Portland

41:357-376 (Sept.) 1950

Aureomycin in Ocular Syphilis. J. E. Poulin.—p. 357.
Acute Intussusception: Report of 9 Cases. O. F. Pomerleau.—p. 359.
Preference of Transverse Incisions in Gallbladder Surgery. R. L. Chasse.—p. 361.
Tuberculosis of Bone Treated with Streptomycin: Case Report. E. J. Smith.—p. 364.
Roentgen Therapy for Treatment of Painful Shoulder. M. F. Lubell. —p. 368.

Medical Annals of District of Columbia, Washington

19:479-542 (Sept.) 1950

Anxiety. R. A. Cohen.—p. 479.
Diagnostic Aids in Coronary Disease Using Exercise with Multiple Chest Leads. J. E. Smith.—p. 485.
Treatment of Venereal Diseases. S. Olansky and G. S. Landman. —p. 491.
Cholecystocolic Fistula: Report of Case. A. F. Castro, G. W. Ault and R. S. Smith.—p. 495.
Albert Freeman Africanus King (1841-1914): His Theory as to the Transmission of Malaria by Mosquitoes. W. B. Daniels.—p. 499.

New England Journal of Medicine, Boston

243:395-430 (Sept. 14) 1950

*Fundamental Consideration of Anticoagulant Therapy. L. B. Jaques —p. 395.
Management of the Neurotic Patient. D. J. MacPherson.—p. 402.
Calcified Leiomyoma of Stomach. J. Garbarini and H. P. Price.—p. 406.
Medical Malpractice. R. Ford.—p. 408.
Neurology. W. K. Jordan and H. H. Merritt.—p. 408.

Anticoagulant Therapy.—The crux of anticoagulant therapy, according to Jaques, is careful control of the drug so as to steer an even course between the dangers of thrombosis and those of hemorrhage. Of the two anticoagulants in general use, heparin acts directly on the blood. It is ineffective by mouth

and must be given parenterally. It acts immediately, and recovery is rapid. This means that control of anticoagulant therapy using heparin is relatively simple. The clotting time will rapidly return to normal when administration is stopped. When a great excess of heparin has been administered through error, an antidote is available in the form of protamine. Bishydroxycoumarin (dicumarol®) acts by interfering with the formation of thrombin by the liver. It increases the prothrombin time but has no effect on the clotting time. The latent period is about 24 to 40 hours. It is long acting. After cessation of treatment with this drug, the prothrombin time may remain prolonged for as long as 10 days. Hence, control is not as easy if overdoses of the drug are given inadvertently. The antidote for overdosage is fresh blood. Large doses of vitamin K neutralize the action of bishyroxycoumarin experimentally but are of less value clinically as an antidote. The author discusses the measurement of the degree of hypocoagulability produced by these drugs and the maintenance of levels of the drugs in the body sufficient to guarantee satisfactory hypocoagulability. He stresses that during treatment with heparin the clotting time must be determined and during treatment with bishydroxycoumarin the prothrombin time must be watched.

New York State Journal of Medicine, New York

50:2095-2222 (Sept. 15) 1950

Health and Medical Services for Agricultural Workers in the Tropics. E. I. Salisbury.—p. 2159.
Appraisal of Industrial Health Examinations. F. H. Shillito.—p. 2163.
Serologic Tests for Cancer. L. J. Boyd.—p. 2167.
Clinical Evalation of Aureomycin, Chloramphenicol and Terramycin. V. Knight.—p. 2173.
Newer Insulins with Special Reference to NPH Insulin. F. B. Peck and W. R. Kirtley.—p. 2182.
Working Minimum of Hepatic Function Tests for Rationalizing Treatment of Jaundice. F. M. Hanger.—p. 2188.
Periodic Disease. B. W. Billow.—p. 2192.
Reduction of Mortality from Abortion. A. H. Rosenthal.—p. 2195.

Pediatrics, Springfield, Ill.

6:173-328 (Aug.) 1950. **Partial Index**

Erythroblastosis Fetalis: I. Problems in Interpretation of Changing Mortality in Erythroblastosis Fetalis. V. C. Vaughan III, F. H. Allen Jr. and L. K. Diamond.—p. 173.
*Use of Parenteral Potassium Therapy in Surgical Patients: Its Role in Preventing Chloride Loss. C. U. Lowe, M. Rourke, E. MacLachlan and A. M. Butler.—p. 183.
Adrenocortical Function in Newborn Infant as Measured by Adrenocorticotropic Hormone-Eosinophil Response. R. Klein and J. Hanson.—p. 192.
Dosage of Drugs in Infants and Children: I. Atropine. K. R. Unna, K. Glaser, E. Lipton and P. R. Patterson.—p. 197.
677 Congenitally Malformed Infants and Associated Gestational Characteristics: II. Parental Factors. J. Worcester, S. S. Stevenson and R. G. Rice.—p. 208.
Closing of Anterior Fontanelle. M. R. Aisenson.—p. 223.
*Neurologic Lesions in Newly Born Infant: I. Preliminary Study; II. Role of Prolonged Labor, Asphyxia and Delayed Respiration. H. M. Keith and M. A. Norval.—p. 229.
Treatment of Thyrotoxicosis in Children with Thiourea Derivatives. R. H. Kunstadter and A. F. Stein.—p. 244.
Studies of Cardiovascular and Renal Systems in Newly Born Infant Using Fluorescein: I. Circulation Time Immediately After Birth. L. B. Slobody, G. D. Rook, M. Levbarg and M. Morcy.—p. 254.
Penicillin and Its Effect in Producing a Predominant Gram-Negative Bacillary Flora in Upper Respiratory Tract of Children. F. D. Haffner, E. Neter and M. I. Rubin.—p. 262.
Pernicious Anemia in an Eight Year Old Girl: Additional Observations in Case Previously Reported as "Nutritional Anemia in Infant Responding to Purified Liver Extract." L. Rosenzweig and O. C. Bruton.—p. 269.
Electroencephalographic Findings in Sickle Cell Anemia. F. S. Hill, J. G. Hughes and B. C. Davis.—p. 277.

Parenteral Potassium Therapy in Surgical Patients.—Lowe and co-workers studied the serum chloride concentration in five surgical patients, two infants aged 21 months and 7 months with intussusception and three children, two with perforated appendix and peritonitis. Material removed by gastrointestinal suction and the urine were analyzed for sodium, chloride, potassium and nitrogen. One of the two children with a perforated appendix received sodium chloride and dextrose, the other a similar regimen, to which potassium was added. Alimentation was entirely by vein. Both children had approximately the same water intake. Results supplemented previous observations by other investigators that following surgical intervention patients may have a low serum chloride concentration. These patients show the effects of fasting, dehydration and potassium depletion owing to an alarm reaction or to alkalosis from loss of gastric chloride. Administration of isotonic sodium chloride solution may be ineffective in accomplishing extracellular repair, because sodium and water go to the dehydrated and potassium depleted cells and the chloride is excreted. More effective physiological hydration of both fluid compartments of the body (chloride being conserved by the kidneys and sodium tending to stay in its proper extracellular position) may be obtained by a decrease in the ratio of sodium to water and addition of potassium. Similar conservation of urinary chloride and elevation in serum chloride has been noted following potassium therapy in patients with low serum chloride concentrations associated with ulcerative colitis, where excessive loss of potassium and chloride in the urine suggests a similar alarm reaction.

Neurological Lesions in Newborn Infants.—Keith and Norval report that 57 (1.3 per cent) of 4,464 infants born in St. Mary's Hospital in Rochester, Minn., in the course of one year, had lesions that affected the nervous system primarily and that were evident during the neonatal period. There were only five among the 57 infants who had plainly difficult births. It seems reasonable to conclude that difficulties during delivery had comparatively little to do with persistent neurological abnormalities in most of the infants who survived. A survey was made of the condition of infants born in the same hospital during two and a half years to determine the relation of prolonged labor, asphyxia and delayed respiration to the occurrence of trauma and, thereby, the relation to neurological lesions of the infant. Prolonged labor appeared to increase the risk of intracranial injury and death of the infant. However, if the infants survived, there was little or no abnorality in subsequent development and no increase in neurological disturbances, at least during the first few years of life. More children had convulsive disorder in the "normal" or control group than in the group of those subjected to prolonged delivery. The same was true among the infants who were asphyxiated; that is, there were more who had convulsive disorder in the control group than among those who were asphyxiated. There were more deaths and more abnormal infants among those who were asphyxiated, but these included many premature infants, of whom many were not viable. If the infants survived the neonatal period, they developed normally, or at least no more abnormalities were noted among those who were asphyxiated than among the controls. Anoxia caused by delay in respiration did not have a serious prognosis in those infants who survived the neonatal period. Even a delay of 11 to 15 minutes, while fatal in two instances, did not appear to cause any abnormality, at least during the first four years of life, in the infants who survived.

Pennsylvania Medical Journal, Harrisburg

53:929-1054 (Sept.) 1950

*Clinical Experience with Mercurital, and Oral Mercurial Diuretic, in Ambulatory Patients. W. D. Stroud, L. B. La Place, J. A. Wagner and I. B. Miller.—p. 953.
Progress Report on American Medicine. E. E. Irons.—p. 957.
Skin Diseases in Children. S. R. Perrin.—p. 961.
Diagnosis of Cancer. R. C. Horn.—p. 966.
Syphilitic Aortitis: Diagnosis by Means of Ascending Aortic Calcification. J. Jackman.—p. 972.
Clinical Aspects of Congenital Heart Disease. R. Ash.—p. 974.
Recent Advances in Anesthesia for Thoracic Surgery: Uses of Procaine Hydrochloride. D. D. Grove.—p. 978.
Malignant Lesions of the Mouth, Lips and Jaw. H. P. Royster.—p. 984.

Mercurial Diuretics in Ambulatory Patients.—Stroud and his associates stress the advantages of oral over parenteral administration of diuretics. They used mercurital, a combination of mersalyl acid and theobromine calcium. They administered this preparation orally for one to eight months to 22 ambulatory patients, who previously required one or two weekly injections of a parenteral mercurial diuretic for the control of congestive heart failure. The orally administered diuretic was found to be as effective as the parenterally administered preparations in the prevention and control of congestive failure in ambulatory patients when given in dosage of one to three tablets daily. Although gastric irritation and nausea appeared to be minimized, this drug, like other preparations orally administered, caused soreness of the gums, abdominal cramps

and diarrhea in certain patients. These untoward effects occurred in six patients in the present series, all of whom were taking two or more tablets daily. They prohibited further use of the drug in four of these patients, and they were adequately controlled in the remainder of the patients by temporary withdrawal of the drug, reduction of dosage and improvement in oral hygiene. The oral use of this diuretic appears preferable to the parenteral administration of mercurial diuretics for ambulatory patients in the absence of individual susceptibility to complicating stomatitis and intestinal disorders.

Plastic and Reconstructive Surgery, Baltimore

6:97-178 (Aug.) 1950. **Partial Index**

Some Half Forgotten Chapters in Development of Plastic Surgery. S. L. Koch.—p. 97.
Mammaplasty, One-Stage Transposition Operation. E. M. Hanrahan. —p. 110.
Late Treatment of Burns. K. M. Mareks and A. E. Trevaskis.—p. 119.
Reconstruction of Scrotum and Skin of Penis. H. May.—p. 134.
*Use and Therapeutic Value of Music in Hospital and Operating Room. K. L. Pickrell, J. T. Metzger, N. J. Wilde and others.—p. 142.
Obliteration of Scars by Shaving. J. E. Sheehan and W. A. Swanker. —p. 153.
*Beryllium Granuloma of Nose: Case Report. V. H. Kazanjian and A. T. Joseph.—p. 156.

Music in Hospital and Operating Room.—Pickrell and his co-workers report on the use of music at Duke Hospital. Facilities for radio reception are provided for patients in their rooms or wards. The authors believed that music might be even more beneficial to patients who are being operated on under local, regional or spinal anesthesia. The comfort and composure of patients was apparent immediately, and their minds were diverted and occupied by the music rather than by the thought of the operation. Since the most suitable music could not always be obtained from the radio and because of the annoyance of static interference from x-ray and other hospital apparatus, record players were used. The authors stress the importance of music as a psychotherapeutic factor in the treatment of all patients, particularly of surgical patients and of children. Music that is slow, restful and suggestive of calm and sleep is usually most desired by patients. Hymns, spirituals and martial music increased the emotional tension in some patients and were the least acceptable. Cushioned earphones exclude all sounds from the operating room, thereby placing the patient, surgeon and assistants at comparative ease, since the possibility of erroneous interpretation of conversation or the development of harmful suspicion is eliminated. A radiophonograph with automatic record changer supplies an almost continuous source of music or reading. Slow revolving unbreakable records are available with essentially unlimited selection of type of music.

Beryllium Granuloma of Nose.—Kazanjian and Joseph describe the case of a man who developed a granulomatous lesion on the dorsum of the nose following laceration by a fluorescent bulb. The wound failed to heal, and it appeared ragged and inflamed. A biopsy specimen revealed a granulomatous reaction suggestive of both sarcoid and of tuberculosis. The lesion was completely excised, with a generous margin of normal skin about it and replaced with a full thickness graft taken from behind the ear. Care was taken to suture the graft to the normal skin margin. Examination of the resected specimen disclosed granuloma of the beryllium type. The graft was completely successful. There was no evidence of recurrence several months later. Beryllium granuloma is best dealt with by wide excision, the wound being grafted or primarily reapproximated, depending on its location.

Rhode Island Medical Journal, Providence

33:389-444 (Aug.) 1950

Body Fluids and Rationale of Fluid Therapy. J. L. Gamble.—p. 403.
Medicine's Concern About Licensure of Medical Record Librarians. C. L. Farrell.—p. 409.

33:445-508 (Sept.) 1950

Asthma in Infancy. W. P. Buffum.—p. 461.
Osteoid Oestoma of Astragalus. S. Spadea.—p. 464.
Sympathetic Nerve Block. E. Damarjian.—p. 466.
Removal of Malignant Kidney Tumor Through Thoraco-Abdominal Incision: Report of Case. J. F. Streker, A. H. Jackvony, W. A. McDonnell and J. E. Farley.—p. 469.

Southern Medical Journal, Birmingham, Ala.

43:755-838 (Sept.) 1950. **Partial Index**

Diagnosis and Management of Chest Tumors. T. H. Burford.—p. 755.
*Results After Operative Removal of Intervertebral Discs. R. T. Odell, R. H. Ramsey and J. A. Key.—p. 759.
Dacryocystorhinostomy: External Approach. M. W. Hester.—p. 766.
Treatment of Premonitory Signs and Symptoms of Ménière's Symptom Complex. R. Harris.—p. 770.
Comparative Study of Certain Vasoconstrictors on Duration of Spinal Anesthesia with Procaine. H. E. Kretchmer and J. Adriani.—p. 771.
Cardiac Arrhythmias During Clinical Anesthesia. W. D. Bennett and M. Davis Jr.—p. 774.
Indications for Cesarean: 10 Year Review. R. N. Creadick.—p. 777.
Adrenocorticotropic Hormone Therapy as Adjunct to Surgery in Chronic Tophaceous Gout. P. D. Doolan, M. C. Cobey and L. H. Kyle. —p. 780.
Trauma to Urinary Bladder in Gynecologic Surgery: Analysis of 61 Injuries. A. Golden and L. Abraham.—p. 783.
Management of Cord Bladder. G. M. Roberts Sr., G. M. Roberts Jr., A. McCravey and W. E. Boehm.—p. 787.
*Panniculitis: Report of Cases. P. E. Jones, J. H. Lamb and L. Goldman. —p. 792.
Surgical Management of Cerebral Abscess Associated with Congenital Heart Disease. D. B. Sweeney and W. B. Patton.—p. 799.
Esophageal Spasm: Report of Unusual Case. N. Van Wezel.—p. 802.
Hormonal Studies in Diabetic Pregnancies. B. F. Keltz, E. C. Keaty and A. A. Heilbaum.—p. 803.
Physiologic Analysis of Psychosomatic Aspect of Peptic Ulcer. A. C. Ivy.—p. 814.

Intervertebral Disks.—Odell and co-workers removed one or more intervertebral disks in 455 patients for the relief of a low back pain and sciatica. Of these, 310 were followed by questionnaire. Satisfactory results were obtained in 277 patients (89.4 per cent) and poor in 33 patients (10.6 per cent). Relief of pain was complete in 136 patients (43.5 per cent). In 141 patients (45.4 per cent), there was slight intermittent pain that did not prevent their return to work. Spinal fusion was seldom done in this series. Myelography was not employed as a routine diagnostic procedure. The operative treatment of ruptured intervertebral disk is a satisfactory procedure when the patient is properly selected and the operation is performed by a surgeon who has learned to do it properly. The results in compensation cases are sufficiently good to warrant surgical treatment of patients with intractable low back and sciatic pain. Surgical intervention should not be advised for any of these patients until conservative treatment has been given a reasonable trial and has failed.

Panniculitis.—Jones and co-workers report the occurrence of panniculitis in three patients, one woman aged 52 and two newborn infants. Panniculitis is an inflammation of the panniculus adiposus. Its origin is undetermined. It was first described by Pfeifer in 1892, and 34 cases have been reported up to 1949. The authors' adult patient noted the appearance of nodules on her arms and legs in association with menstruation. The lesions broke down and underwent liquefaction necrosis, discharging a purulent, oily material after the patient was given a series of roentgen treatments to curb excessive menopausal bleeding. It seems possible that the radiation may have upset the hormonal balance and that this in turn changed the reaction in the fat tissue. The patient's course was progressively downhill, with new lesions appearing on the arms, abdomen, buttocks and thighs. Large pieces of necrotic tissue sloughed out of the affected areas. The patient died seven weeks after admission to the hospital. Necropsy showed fatty degeneration of the liver cells and necrosis. Fat necrosis of the newborn was observed in the two infants. The fever in the female infant was found to be due to an associated ear infection, while prolonged elevation of temperature and anemia in the male infant were apparently part of the fat tissue changes, since no secondary infection of the involved areas themselves or of other tissues was observed. The second infant underwent a severer type of change, with greater local disturbance, entailing more systemic reaction. The first infant's mother was a known diabetic, while fat embolism was suspected in the death of the mother of the second infant, although this was not confirmed by necropsy. A congenital abnormality of fat tissue enzymes may be the causative factor in cases of Weber-Christian disease in the newborn. Several authors advanced the hypothesis that some disturbance of the nutrition or of the metabolism of fat cells so changes the nature of normal fat that it acts as a foreign body, bringing about the inflammatory reaction and degenerative alterations characteristic of an invasion of foreign body giant cells.

FOREIGN

An asterisk (*) before a title indicates that the article is abstracted.
Single case reports and trials of new drugs are usually omitted.

Australian and New Zealand J. Surgery, Sydney

20:1-84 (Aug.) 1950

Medicine and the Humanities. J. Medley.—p. 1.
Cerebral Angiography in Neurosurgery. J. L. Dowling.—p. 11.
Gas Cysts of Intestine. E. S. J. King.—p. 25.
Treatment of Traumatic Ulnar Neuritis: Mobilization of Ulnar Nerve at Elbow by Removal of Medial Epicondyle and Adjacent Bone. T. King.—p. 33.
Ocular Palsies Associated with General Diseases. T. K. Lyle.—p. 43.
Hypospadias. K. B. Fraser.—p. 52.
Surgery of Inferior Oblique at Its Scleral Insertion. C. Colvin.—p. 59.
Treatment of Carcinoma of Breast. V. M. Coppleson.—p. 65.
Operation for Undescended Testes in Superficial Inguinal Pouch. C. Craig.—p. 69.
Four Unusual Complications of Partial Gastrectomy. J. P. Fleming and J. N. Ward-McQuaid.—p. 73.

British Journal of Tuberculosis, London

44:55-81 (July) 1950

Case of Malignant Thymic Tumour Associated with Chronic Pulmonary Tuberculosis. M. Davidson.—p. 55.
Arterio-Venous Aneurysm of Lung with Pulmonary Tuberculosis: Report of Case. C. K. Robertson.—p. 58.
Brompton Rehabilitation Clinic. N. C. Oswald.—p. 61.
Results of Pneumoperitoneum in Pulmonary Tuberculosis. E. W. Thompson Evans.—p. 67.
Massive Hæmothorax in Artificial Pneumothorax Treated with Streptokinase. R. G. Gauld and J. T. Harold.—p. 77.

Edinburgh Medical Journal

57:265-316 (July) 1950

Bronchial Adenoma. B. Dick.—p. 265.
Cancer and Translation of Influences into Causes. M. Copisarow.—p. 270.
Aetiology of Mental Illness. J. J. de Villiers.—p. 275.
Penicillin Inactivators and Susceptibility of Micro-Organisms to Penicillin. J. W. Czekalowski.—p. 281.
Unusual Neurological Symptoms in Polycythaemia Rubra Vera. A Grunberg, J. L. Blair and R. M. Rawcliffe.—p. 305.

Lancet, London

2:381-424 (Sept. 23) 1950

*Liquorice Extract with Deoxycortone-Like Action. J. A. Molhuysen, J. Gerbrandy, L. A. de Vries and others.—p. 381.
*Diagnostic Value of Increased Urinary Output of Noradrenaline and Adrenaline in Phaeochromocytoma. A. Engel and U. S. von Euler.—p. 387.
Refractory Hypochromic Anaemia and Steatorrhoea: Treatment with Intravenous Iron. C. F. Hawkins, A. L. P. Peeney and W. T. Cooke.—p. 387.
*Enhancing Effect of Cortisone on Tuberculosis in Mouse. P. D'Arcy Hart and R. J. W. Rees.—p. 391.
Treatment of Fibrositis with Adrenaline, Ephedrine, and Belladonna Creams. T. H. Howell.—p. 395.
Interpretation of Histamine and Insulin Tests in Patients with Peptic Ulceration. J. N. Hunt.—p. 397.

Licorice Extract with Deoxycortone-Like Action.—According to Molhuysen and his associates, Revers reported from the Netherlands that many patients with peptic ulcer improved after taking a proprietary preparation that consisted of a mixture of succus liquiritiae, fructus anisi and ferrum reductum. The majority of the patients became symptom free within a short time. Roentgen examination revealed that sometimes a deep ulcer of the lesser curvature disappeared within three weeks. Edema developed in one out of every five patients treated; many complained of a headache, and some noticed shortness of breath and abdominal pain. It was ascertained that the edema-producing factor was either glycyrrhizin or some substance precipitated with it by acid. The effects observed were similar to those following injection of large doses of deoxycortone or of injection of pituitary adrenocorticotropic hormone (ACTH). Apparently succus liquiritiae and the purified product contained a substance similar in action to that of one of the two hormones. The substance was active when taken by mouth. The authors studied the urinary output of sodium, potassium and creatinine after the administration of the hormones and of succus liquiritiae. They emphasize, especially in elderly patients, the harmful effects of potassium loss on the myocardium, which is overburdened by the increased venous pressure and by the considerable rise in blood pressure. The occurrence of cardiac asthma in subjects using licorice in sweets or in drugs is thus explained. The effect of a licorice extract taken by mouth is similar to that of injection of large doses of deoxycortone, but it lasts longer. The blood pressure tends to remain elevated after discontinuance of the drug unless a salt-free diet is used. The retention of water and sodium chloride during treatment with deoxycortone, pituitary adrenocorticotropic hormone or succus liquiritiae is self limiting, in subjects with normal heart and kidneys, because the rise in venous pressure leads to an increase in cardiac output, which induces a saline diuresis. A patient with Addison's disease who did not respond to pituitary adrenocorticotropic hormone did not respond positively to succus liquiritiae. There was a slight negative response. A patient with rheumatoid arthritis who responded favorably to pituitary adrenocorticotropic hormone showed an insignificant improvement, or none, after the use of succus liquiritiae.

Increased Urinary Output of Arterenol and Epinephrine in Pheochromocytoma.—According to Engel and von Euler, epinephrine (adrenalin®) and other catechol derivatives, when administered to man, are partly excreted in the urine in a conjugated form. Since catechol derivatives may be extracted from urine and estimated quantitatively in a comparatively simple way (Euler and Hellner, 1950), it appeared that an increased formation and output of such substances could be used as basis for the diagnosis of pheochromocytoma. The authors cite two patients who showed a greatly increased arterenol-epinephrine output in the urine. In the first case, a tumor situated at the bifurcation of the abdominal aorta and weighing 48 Gm. was removed. Histological examination revealed a typical pheochromocytoma. In the second case a tumor weighing 20 Gm. was removed from the left suprarenal. The relative contents of the catechols in the two tumors were also borne out by paper chromatography. The proportions of arterenol and epinephrine in the urine were approximately the same as in the tumors.

Cortisone and Tuberculosis in Mice.—D'Arcy Hart and Rees produced in mice a chronic pulmonary tuberculous infection sufficiently stable to serve as a test infection. Intravenous injection of 0.0006 mg. dry weight of human type tubercle bacilli produced in mice an infection that was relatively nonprogressive over six to 12 weeks and was characterized during this period by small, discrete, predominantly proliferative, pulmonary lesions containing scanty tubercle bacilli. A daily dosage of 0.25-05 mg. of cortisone given subcutaneously for two to three weeks during the stable period of this chronic pulmonary infection greatly exacerbated the disease, with a resulting high mortality. The voluminous lungs now contained large coalescing necrotic lesions with great numbers of tubercle bacilli. The more acute type of tuberculous infection in the mouse, produced by intravenous injection of 0.06 mg. of bacilli, was also aggravated by 0.5 mg. daily of cortisone, given from the first until the ninth day of infection. The chronic infection test proved highly satisfactory as a method for demonstrating increased susceptibility to tuberculosis due to cortisone. The acute infection test was more difficult to interpret. The effect of cortisone on murine tuberculosis is not likely to be due to depression of allergy or of collagen formation. Although human tuberculosis differs considerably from the murine form, and the present dosage of cortisone was relatively high, these observations should be kept in mind since tuberculosis in man may possibly be similarly aggravated.

Annales Paediatrici, Basel

175:223-284 (Sept.) 1950

Hepatic Cirrhosis with Dwarfism and Hypophosphatemic Rickets in Early Childhood: Contribution to Problem of So-Called Hepatic Rickets. A. Eckstein.—p. 224.
"Healing" of Infant with Pneumococcus-Meningitis. C. de Lange.—p. 235.
*Effect of Interrupted Penicillin Therapy in Acute Suppurative Otitis, with Special Reference to Otitis in Children. T. Jersild and F. Kiørboe. —p. 250.
Aerosol-Penicillin Therapy for Infant and Children. P. Karlberg, G. Sterner and G. Wallmark.—p. 263.
*Human Hyperimmune Serum and Streptomycin for Treatment of Whooping Cough in Infants and Young Children. F. Hatz and C. Burckhardt.—p. 274.

Interrupted Penicillin Therapy in Suppurative Otitis.—The interrupted administration of penicillin employed by Jersild and Kiørboe consists in giving only two doses each day, instead of giving it every three or four hours, as is customary with other clinics. The individual doses for infants less than 1 year old were 60,000, for those between 1 and 5 years, 90,000, for those between 5 and 15 120,000 and for those over 15 years, 150,000. The authors treated 266 patients with 385 suppurating ears. The otitis was a sequel of scarlet fever in about two thirds of the patients. Hemolytic streptococci were the organisms most frequently demonstrated in the ear secretions. The organisms usually disappeared in one day in the children treated with penicillin but persisted for an average of 20 days in those not given this drug. Discharge from the ear continued for 6.5 days in the treated and for 36.5 days in the untreated group. Ear operations were required in 3.5 per cent of the treated and in 30.3 per cent of the untreated patients. Follow-up revealed that a relapse of the lesion appeared within three months in about one fourth of all the patients. The frequency of relapse was considerably higher for patients under three years than for those over three. The hearing acuity appears to have remained normal in those patients who had no relapse. Interrupted penicillin therapy has given excellent results in suppurative otitis in children.

Human Hyperimmune Serum and Streptomycin in Whooping Cough.—Hatz and Burckhardt report observations on 50 children with whooping cough, aged up to two years. Streptomycin was given to 25 of these. Streptomycin and human hyperimmune serum was given to the other 25 patients. The serum was obtained from healthy adults who had been immunized with a concentrated pertussis vaccine and who had whooping cough. The gamma globulins of 20 cc. of the serum of these persons are contained in 2.5 cc. of the serum. The results obtained were compared with a group of 50 of the same age (up to two years), who during the years 1946-1947 were treated chiefly with ascorbic acid. The number and severity of attacks were greatly reduced, and the general health and appetite quickly improved in the group treated with streptomycin alone, and these results were accentuated in the group treated with streptomycin and human hyperimmune serum. When complications did arise, they tended to disappear more quickly in the streptomycin-treated group. The only side effects observed were rashes in six cases. These were either rubeoliform or scarlatiniform. Treatment with hyperimmune serum and streptomycin combined is to be recommended in young infants and for grave complications of older children.

Deutsche medizinische Wochenschrift, Stuttgart

75:1061-1108 (Aug. 25) 1950. **Partial Index**

Examination of Circulatory Function in Surgery. F. Meissner.—p. 1061.
Intestinal Gangrene. H.-J. Lössl.—p. 1066.
*Action of Caffeine in Patients with Hypertension. I. Sebök.—p. 1067.
Amyotrophic Lateral Sclerosis After Polyarthritis. W. Köhler.—p. 1070.
*Etiology of Puerperal Mastitis: Experimental Studies. H. Muth.—p. 1072.
Postoperative Cutaneous Emphysema After Laparotomy. R. Mey.—p. 1074.

Action of Caffeine in Hypertension.—According to Sebök, it is the accepted opinion that caffeine causes a general vasoconstriction and an increase in blood pressure. In the brain, heart and kidney, it produces vasodilatation. The author attempted to ascertain whether the hypertensive effect of caffeine was a degree sufficiently great to cause caffeine to be withheld from patients with hypertension. Administration of 0.05 or 0.1 Gm. of caffeine to 31 patients with hypertension had the effect of lowering the systolic and the diastolic blood pressures. The fall amounted to from 10 to 80 mm. of mercury in the systolic pressure. Maximal decrease in pressure was usually observed from 40 to 50 minutes after the administration of caffeine. In about three fourths of the patients the pressure had not returned to the initial values two hours later. Administration of caffeine in controls with normal blood pressure produced either a slight elevation in pressure or a reduction, as in the hypertensive patient. These investigations and the fact that caffeine dilates the coronary vessels and thus improves the metabolism of the myocardium suggest that there is no justification for interdicting either caffeine or coffee in patients with hypertension.

Etiology of Puerperal Mastitis.—Muth states that his investigations and those of others indicate that the Staphylococcus aureus hemolyticus is the most frequent cause of puerperal mastitis. Bacterium coli and hemolytic streptococci rarely cause mastitis. The Staph. aureus hemolyticus is frequently found in the nasopharynx of infants. Some investigators assume that this organism is transferred to the maternal breast from the mouth of the infant and serves as the causal factor in mastitis. Bacteriologic studies were made at the author's clinic on 200 puerperal women and their infants. Smears were obtained from the nose and pharynx of 100 women during delivery and 48 hours later and from their infants 48 hours after delivery. In another group of 100 women the bacterial flora of the maternal nasopharynx, the nipple and the vagina was studied during delivery and seven days later and was compared with that of the nasopharyngeal flora of the infants seven days after birth. Seven days after delivery Staph. aureus hemolyticus was found on 87 per cent of the maternal nipples and at the same time in the nasopharynx of 99 per cent of their infants. Further observations suggested that the staphylococci were transferred from the nasopharynx of the infants to the nipple. The infants seem to receive this organism from the nasopharynx of the mothers or the nurses or from the vagina of the mother. Measures designed to interrupt this cycle promise to be of prophylactic value. The author cites one investigator who reduced the incidence of mastitis to 0.1 per cent by applying a sulfathiazole powder to the nipples of nursing mothers.

Monatsschrift für Kinderheilkunde, Berlin

98:329-368 (Aug.) 1950. **Partial Index**

*Toxoplasmosis in Infants. H. Walenz and A. Westphal.—p. 329.
Physical and Bacteriologic Studies on Adsorbent Chemotherapeutic Substances That Contain Pectin: Their Use in Dyspepsia in Nurslings. M. Debusmann.—p. 336.
Gastrospasm: Therapeutic Trials with Ultrasonic Waves. D. Helbig. —p. 345.
Etiology and Therapy of Seborrheal Dermatitis. H. Lemke.—p. 350.

Toxoplasmosis in Infants.—Walenz and Westphal observed during the past year eight infants with suspected toxoplasmosis. The diagnosis could not be corroborated in four. Of the four patients with proved diagnosis of toxoplasmosis, three had hydrocephalus, alterations in the cerebrospinal fluid, neurological symptoms and lesions in the eyegrounds. These symptoms were described in the literature as indicative of congenital toxoplasmosis. In the fourth patient, only cerebrospinal fluid changes and chorioretinitis suggested toxoplasmosis. The intracerebral calcifications mentioned in the literature as being characteristic of congenital toxoplasmosis could not be ascertained by roentgenoscopy in these patients. Serologic verification of toxoplasmosis was possible in all four by means of the Sabin-Feldman serum dye test. Examination of blood specimens gave positive titers in all the infants and their mothers. This fact suggests intrauterine transmission. The parasites of toxoplasmosis in two of the infants could be demonstrated either directly from the sediment of the cerebrospinal fluid or after concentration in several animal passages. Although toxoplasmosis may attack any organ, in infants the parasite seems to have greatest affinity for the central nervous system. Various therapeutic methods have proved largely ineffective. Intrauterine death results in many cases in which toxoplasmosis is transmitted from the mother to the fetus. If the pregnancy is carried to term, hydrocephalus and other serious lesions often cause death during early infancy.

BOOK NOTICES

The reviews here published have been prepared by competent authorities and do not represent the opinions of any official bodies unless specifically stated.

Multiple Sclerosis and the Demyelinating Diseases. Proceedings of the Association, December 10 and 11, 1948, New York. Research Publications, Association for Research in Nervous and Mental Diseases, Volume XXVIII. Editorial Board: Henry W. Woltman, M.D., H. Houston Merritt, M.D., S. Bernard Wortis, M.D., Clarence C. Hare, M.D. Cloth. $12. Pp. 675, with 153 illustrations. The Williams & Wilkins Company, Mount Royal & Guilford Aves., Baltimore 2, 1950.

This is the second volume on multiple sclerosis which has been issued by the Association for Research in Nervous and Mental Diseases, the first having appeared in 1921. This volume consists of 40 papers contributed by 68 authors, covering the general subjects of history, ecology, etiology, blood flow, anatomy and chemistry, pathology, clinical aspects and treatment and rehabilitation in multiple sclerosis. The foreword, by H. Houston Merritt, S. Bernard Wortis and Henry W. Woltman, is an admirable summary of the present status of the multiple sclerosis problem, although it presents as established fact some of the wholly tentative statistics on incidence and prevalence, based on a single study made in Rochester, Minn.

Walter Timme, in the first paper in this volume, discusses the history of multiple sclerosis and summarizes the findings and conclusions of the 1921 meeting of the association. This paper serves as an excellent introduction and background to the remainder of the volume. In the section on ecology of multiple sclerosis (which would ordinarily be called epidemiology), Charles C. Limburg presents an analysis of mortality statistics; Alexander R. MacLean, Joseph Berkson, Henry W. Woltman and Louise Schionneman report on a study of the population of Rochester, Minn., and Lawrence C. Kolb reports on studies made in the Eastern Health District in Baltimore. In general, Limburg agrees with the hypothesis that mortality from multiple sclerosis is positively associated with a cold climate, although the evidence he presents is not entirely convincing. These three papers present varying estimates of the prevalence of multiple sclerosis of 35, 55 and 15 cases per 100,000 population. Kolb states that in the Eastern Health District there were twice as many patients, over a 10 year period, seeking aid for multiple sclerosis as for residual paralysis following acute poliomyelitis. He notes that there were little or no attempts at rehabilitation, many patients occupying hospital beds for long periods, and that the medical services provided for these patients were chiefly diagnostic. The discussion of these papers brought out the observation that there was apparently considerable difference in disability and mortality between private patients and clinic and ward patients.

Hans H. Reese discusses the theories concerning the etiology of multiple sclerosis, points out the probability that the etiological factors are multiple and discusses the various theories under the headings of infection, venular thrombosis, vascular spasm, allergy and nutrition. Roland P. Mackay, in a discussion of the familial incidence, concludes that there is a familial factor which is insufficient by itself to produce the disease. Tracy Putnam's review of the pathogenesis of multiple sclerosis, if accepted, points to injuries, infections, a cold, damp climate and pregnancy as factors precipitating acute exacerbations. In treatment, Putnam recommends the use of bishydroxycoumarin (dicumarol®) and diphenylhydantoin (dilantin®) sodium as promising agents in prevention of acute episodes. (A more recent critical review of the subject by George A. Schumacher [THE JOURNAL, Aug. 5, 1950, p. 1241] rejects the evidence for these conclusions as inadequate.) The clinical features of multiple sclerosis are well analyzed in a report by Sidney Carter, Daniel Sciarra and H. Houston Merritt of 56 cases proven by autopsy.

An interesting discussion of the role of psychodynamic factors in the etiology of multiple sclerosis is comprised in three papers on the subject by Roy R. Grinker, George C. Ham, Fred P. Robbins; by R. Harrower, and by Francis J. Braceland and Mary E. Giffin. Grinker and his associates describe what they consider a characteristic premorbid state of multiple sclerosis as that of "great immaturity since early infancy," a strict mother, a nondominant father, absence of warm relations with other people, no free anxiety and a precipitating factor for overt symptoms of some major change in the life situation. Braceland and Giffin, on the other hand, conclude that there are no specific characterologic personality changes in multiple sclerosis. Harrower, on the basis of a battery of psychological tests, concludes that patients with multiple sclerosis show less anxiety over their disability, more acceptance of dependency, less awareness of conflict and an excessive cordiality, as compared with control groups. Otto R. Langworthy, in his paper on maladjustment problems in multiple sclerosis, concludes that "we have no clear evidence at present that emotional factors can contribute to the development of the lesions of multiple sclerosis through change in blood vessels or otherwise."

This is a volume well worth reading for anyone interested in the problem of multiple sclerosis. It is to be hoped that a summary of the apparently established facts, especially with regard to diagnosis and prognosis, will be made available to the general practitioner, who very much needs to know of the importance and of the relatively more hopeful aspects of this widespread disease.

Chirurgie der Urogenitalorgane: Indikation und Technik. Von Prof. Dr. H. Boeminghaus. Band I: Nieren, Harnleiter. Band II: Blase, Prostate, Samenblasen, Hoden, Nebenhoden, Samenstrang und Skrotum. Band III: Penis, Harnröhre, Anhang, Neuro-chirurgische Eingriffe bei Erkrankungen der Urogenitalorgane. Cloth. Pp. 251; 243; 228, with 519 illustrations. Werk-Verlag Dr. Edmund Banaschewski, (13b) Bad Wörishofen, 1950.

Book 1 describes surgery of the kidneys and ureters; book 2, surgical treatment of the urinary bladder, prostate, seminal vesicles, testes, epididymis, spermatic cord and scrotum; book 3, surgical procedures employed for pathologic conditions of the penis and urethra. An appendix on neurosurgical procedures in therapy of the urogenital apparatus is included.

It is obviously impossible to enter into a detailed analysis of all the procedures described. However, the over-all impression, after thorough reading, is favorable, for the work is of a practical nature, dealing particularly with the indications for operation in cases of diseases of the genitourinary apparatus and the surgical technic best adapted thereto. It is obvious, as the author points out, that didactic text and artistic illustrations, no matter how excellent in themselves, are never sufficient to create a surgeon; practical experience must supplement theoretical knowledge. Evaluated on these premises, the work serves an excellent purpose. The text is thorough, and the illustrations profuse. Most of the latter are diagrammatic, but all are adequate and clear.

It seems that, since the war years restricted scientific intercourse in European countries, there is a keen desire among surgeons there to keep abreast of modern surgical procedure. The fact is well evidenced in this work, for the procedures are admirably presented, without padding. The literature is abstracted exceptionally well; in the section on surgery of the prostate, Millin's procedure is particularly well described and illustrated. In his discussion of urinary incontinence, the author does not limit himself to consideration of surgical procedures adapted to the male patient but includes those employed for the female patient as well. In the appendix, one finds ably presented sections dealing with elimination of pain in operations on the kidney, bladder, prostate, rectum and external genitalia, with the approach in treating oliguria, anuria and uremia and with various procedures used in the treatment of impotentia generandi. A conservative analysis of the so-called reactivation

procedures for senility is also given. The experimental work of Harms, Steinach, Sand and others is thoroughly analyzed, with the conclusion that transplantation of testicular material will give results only when there is definite evidence of organic failure of internal secretion of the testes. A conservative attitude is taken here, as well as in analysis of the results of the Steinach procedure. Postoperative complications are well presented, as are the neurosurgical procedures related to pathological conditions of the genitourinary apparatus, as: renal denervation, the surgical treatment of hypertension as related to renal pathology, resection of the hypogastric nerves, chordotomy and alcohol injections for the relief of pain.

Those who read German will find this work a worth while addition to their libraries. This applies to the student, the general surgeon and the specialist as well.

B.C.G. Vaccination in Theory and Practice. By K. Neville Irvine, D.M., M.A., B.Ch., Medical Superintendent, Smith Isolation Hospital, New York City. With a Foreward by Konrad Birkhaug, B.A., M.Sc., M.D., Chief of the B.C.G. Laboratory, New York State Department of Health, Albany. Cloth. $3; 9s.6d. Pp. 130. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill.; Blackwell Scientific Publications, 48 Broad St., Oxford, England; The Ryerson Press, 299 Queen St., W., Toronto 2B, 1949.

Since the introduction of BCG vaccine and its first use in 1922 in infants, probably no preventive measure for the control of tuberculosis has aroused so much controversy. This book attempts to review the literature on BCG vaccination and to give practical details of the technic of vaccination. The evolution of the BCG strain is traced. The theory underlying BCG vaccination is stated, and the various methods of vaccination used at different centers are detailed. The stability of the virulence of BCG and the safety of the vaccine are considered. There is also an effort to investigate the degree of resistance produced by the vaccination, and consideration is given to the practical aspects of BCG vaccination. The material is clearly presented throughout the book.

There are, however, many who will disagree with the author's statement that "At long last BCG vaccination has been universally accepted as a valuable weapon for our armament in the fight against tuberculosis." The author leaves unanswered the question of the efficacy of BCG vaccine but believes that the exact degree of efficacy is important only if the BCG vaccine is to be used to replace any of the well accepted antituberculosis measures.

Tissue Culture Technique. By Gladys Cameron. Second edition. Cloth. $4.20. Pp. 191, with 54 illustrations. Academic Press, Inc., 125 E. 23rd St., New York 10, 1950.

Contrary to the popular belief that tissue culturing is a recent innovation in medical science, the fact is that in vitro growth of tissues was accomplished in the latter part of the last century. Improved and modified technics have subsequently been developed according to the type of cellular activity under study.

Tissue culture consists of aseptic transfer of tissues from a living organism to an in vitro environment which provides optimum conditions of nutrition, aeration and temperature for cell proliferation, organization and function. Catabolic products necessarily must be removed to prevent death of the cells, and nutrients must be supplied in excess. The author obviously is cognizant of the difficulties encountered in the practical procedures outlined and has painstakingly incorporated details of technic which both the beginner and advanced worker will appreciate. Too often technical details are not given in published procedures; this results in waste of materials, loss of time and frustration of the investigator. The author stresses the need for knowledge of cytology to insure proper interpretation of results obtained by these technics.

The volume is a practical laboratory guide for the culture of tissues. It emphasizes the fact that the technics are relatively simple and require little specialized equipment but demand technical skill and knowledge of normal cytology of the cultured material. In addition to the technical procedures, the volume contains chapters on micromanipulation of tissue cultures, histological technics and photomicrography of tissue cultures. An extensive bibliography and a list of suppliers of special equipment are appended.

The Diagnosis of Salmonella Types. By F. Kauffmann, M.D., Chief, International Salmonella Center, State Serum Institute, Copenhagen, Denmark. Publication Number 62, American Lecture Series, A Monograph in American Lectures in Tests and Techniques. Edited by Gilbert Dalldorf, M.D., Director of the Division of Laboratories and Research, New York State Department of Health, Albany, New York. Cloth. $2.25. Pp. 86. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill.; Blackwell Scientific Publications, Ltd., 49 Broad St., Oxford, England; The Ryerson Press, 299 Queen St., W., Toronto 2B, 1950.

Diarrhea, typhoid and paratyphoid fevers, food poisoning, bacteremia, bone infections and even infections of the central nervous system are manifestations of the pathogenicity of the Salmonella group in man. The organisms are also found in rodents, horses and birds, including chickens. Differentiation of typhoid from paratyphoid fever and the incrimination of the agents responsible for gastroenteritis caused by Salmonella necessarily are dependent on isolation and identification of the organisms. Salmonella typing has considerable epidemiological value. Immunologic differentiation of these organisms has been emphasized since the 1920's; prior to that time they were separated on the basis of physiological characteristics. An absurd number of new species have been described solely on the basis of immunologic differences; it now appears more logical to subdivide the serotypes into biochemical types by biochemical methods, and this is the author's approach. This handbook incorporates details of methods for preparing antigens, vaccines and immune serums, performance of agglutination and absorption tests, tables for identification of antigens and methods for serologic diagnosis. An appended section indicates types of media, with formulas which the author considers optimum for the procedures employed. The author is an authority in this field, having been appointed chief of the International Salmonella Center at the State Serum Institute, Copenhagen, Denmark, established by the World Health Organization in 1948. Several American state health departments have been designated to collaborate with the International Center for the collection and identification of Salmonella strains.

Counseling the Handicapped in the Rehabilitation Process. By Kenneth W. Hamilton, Associate Professor of Social Administration, Ohio State University, Columbus. Cloth. $3.50. Pp. 296, with 4 illustrations. The Ronald Press Company, 15 E. 26th St., New York 10, 1950.

This is a textbook written by a well qualified teacher in the field of rehabilitation. The book is written for "all who counsel the handicapped on their problems—social workers, psychologists, physicians, therapists, and employment counselors." It is documented fully and has many interesting illustrations.

The text emphasizes the role of the rehabilitation counselor in bringing to the use of the disabled person "individualized and coordinated professional services." Emphasis is placed on considering the total needs of the disabled person—physical, mental, social, vocational and economic. The book begins with a discussion of the nature and purpose of rehabilitation, then covers the rehabilitation process and development of community resources and finally treats the problem of the evaluation of the results of rehabilitation. As may be apparent, the rehabilitation theme is developed logically and in this regard probably represents the best systematization to appear to date. There is an interesting treatment of the distinction between disability and handicap, basic in the development of a rehabilitation program. Physicians may feel that insufficient attention is given to medical-physical factors in chapter 4 where areas to be studied are discussed, but close perusal will show that there is as much coverage as is given to psychological and emotional, educational, social and vocational factors. Particularly important to physicians interested in community aspects of rehabilitation are chapters 7 through 10, dealing with such topics as community organization, the severely handicapped in the local community and the rehabilitation center. The central theme of the book is contained in chapter 8, on the rehabilitation counselor. Here, stress is placed on the need for special training programs for this new specialty for which current programs in social casework and vocational counseling are inadequate in the opinion of Professor Hamilton.

Some may disagree with the emphasis given to the selection of suitable employment as the "crowning achievement of the rehabilitation process" and feel that sufficient recognition of

self-care as a goal is not appreciated fully. However, Professor Hamilton is concerning himself with the majority of disabled persons and demonstrates adequately his understanding of setting other goals for the severely disabled. This book should be found in the libraries of any physician interested in the process of rehabilitation at the community level. Its systematic approach to the problem is to be recommended highly.

The Cerebral Cortex of Man: A Clinical Study of Localization of Function. By Wilder Penfield, C.M.G., M.D., B.Sc., Professor of Neurology and Neurosurgery, McGill University, Montreal, and Theodore Rasmussen, M.D., Professor of Neurological Surgery, The University of Chicago, Chicago. Cloth. $6.50. Pp. 248, with 121 illustrations. The Macmillan Company, 60 Fifth Ave., New York 11, 1950.

This book is based on the Lane Medical Lectures which Penfield gave in 1947. Four hundred craniotomies performed between 1928 and 1947 presented the opportunity to stimulate variods parts of the cerebral cortex with electrical currents and to record the objective (movements) and subjective effects. The results of these studies are presented clearly and with the necessary details. Objective results and interpretation are sharply separated. The investigations give a very complete description of the organization of the sensorimotor cortex. The primitive character of the movements is emphasized. They are "not more complicated than those the newborn infant is able to perform." Evidence of the existence of a secondary motor cortex is also presented. A certain muscle may show widely separated cortical foci when it is used in different functional groupings. Central overlap exists clearly in precentral and postcentral gyrus. The authors assume that the diencephalon plays an important role in the elaboration of movements. A considerable part of the book is devoted to observations on the effect of stimulation of nonmotor areas. Perhaps the most interesting phenomenon which Penfield and Rasmussen discovered is the fact that electrical stimulation of the temporal lobe elicits illusions, hallucinations and dreamlike conditions which suggest that the temporal lobe plays an important role in memory. Whereas stimulation of the sensorimotor parts of the brain results only in primitive movements or sensations, that of the temporal lobe activates "acquired synaptic patterns." The book is one of the most important contributions to neurosurgery and physiology which has appeared in many years. It is beautifully printed and illustrated.

Human Milk: Wartime Studies of Certain Vitamins and Other Constituents. By S. K. Kon and E. H. Mawson. Medical Research Council Special Report Series No. 269. Paper. 4s. Pp. 188, with 19 illustrations. His Majesty's Stationery Office, York House, Kingsway, London, W.C.2, 1950.

This study is an important contribution. It advances greatly our knowledge of the composition of individual samples as influenced by such factors as the mother's state of nutrition, the stage of lactation, the milk yield, the season of the year, the age and parity of the mother. The report is well planned for ready reference. It is divided into two chief sections. One deals with the constituents of human milk and the other with the relation between the constituents studied and nutritional standards. Tables and figures are used to good advantage. The language is clear and concise and easily read. Each subsection is followed by a bibliography of related studies. The report is summarized in a few short pages at the end of the book.

It is impossible to illustrate the many points of special interest to pediatricians, obstetricians and public health workers which are brought out in this book. However, the book is inexpensive and can be easily obtained by all professional persons who are concerned in any way with the problem of lactation. Nevertheless, for purposes of illustration, attention is called to the fact that it may be misleading to apply to human milk conclusions drawn from the study of cow's milk. For example, the vitamin A content of human milk, which is initially high, falls rapidly the first three weeks and then falls gradually, until it reaches one third of the original value. On the other hand, thiamine increases rapidly until it levels off at the fifth week. This is the reverse of what happens with the cow. Seasonal variations are likely to be noted in the vitamin A content of cow's milk, whereas this does not seem to be true of human's milk. This study is an impressive achievement.

Saints, Sinners and Psychiatry. By Camilla M. Anderson, M.D. Assistant Clinical Professor of Psychiatry, University of Utah, Salt Lake City. Cloth. $2.95. Pp. 206. J. B. Lippincott Company, 227-231 S. 6th St., Philadelphia 5; Aldine House, 10-13 Bedford St. London, W.C.2; 2083 Guy St., Montreal, 1950.

This book appears to confirm the idea that under the critical eye of the psychiatrist "normal" as applied to behavior of the struggling human race is an adjective tolerated only in honor of tradition. Unlike so many authors in this field, Anderson does not hem and haw in polysyllabic jargon. She says directly what she wants to say, in language easy to understand. Case histories are presented without customary drawn-out discussion; they portray the essentials in one or two paragraphs, without the irrelevant fantasy and romance so frequently encountered in psychiatric reports.

The book presents a novel and sensible interpretation of the dynamics of human behavior. It postulates that behavior is a culmination of psychological structure and function. Structure involves the individual as a personal entity with all the psychological components of a human being striving toward recognition. Function is an expression of these components, and the cumulative result sets the pattern of behavior. Illustrations of this mechanism follow:

Structure	Function
I am the baby	I get special consideration
I am the oldest	I get the hardest jobs
I am smart	I get approval
I am dumb	I get picked on
I am a nuisance	I get attention
I am honest	I get approval
I don't trust people	I don't get disappointed
I am a sissy	I get Mamma's love
I am selfish	I get something
I am different	I don't have to compete
I am fatherless	I mean more to women
I am awkward	I am relieved of many jobs
I am mistreated by father	I get more from mother

Throughout childhood, behavior is modeled in accordance with the approval-disapproval reactions shown by the persons significant to the growing organism. Parents, siblings, grandparents, aunts, uncles, teachers and playmates all exert their influence on the ultimate character of the person. And being, as everyone was and indeed remains, at the mercy of so motley a combination of personalities, is it any wonder that everybody is neurotic? Saints or sinners, we are all the product of our early environment—a concept not too different from the Watsonian prince-pauper conditioned-reflex theory of a quarter of a century ago.

The book was apparently meant for popular use. The physician, however, will find it interesting. It is full of wholesome material for daily application in sociomedical study and psychosomatic medicine, and can be recommended for its instructive features and practical philosophy as much as for its delightful style and easy readability.

Studies in Population: Proceedings of the Annual Meeting of the Population Association of America at Princeton, New Jersey, May 1949. Edited by George F. Mair. Paper. $2.50. Pp. 169. Princeton University Press, Princeton, New Jersey, 1949.

This book will be of interest and value to those persons interested in our current and future population problems and trends. The five sections of the book represent the five sessions of the meeting: two on current problems and technics, one on food resources and two on fertility. The first section, Application of Demographic Data to Current Problems, contains papers on the relative importance of mortality and divorce in the United States, on the length of the working life and on a series of illegal abortions. One speaker pointed out that, in view of the rapid rise of the divorce rate during recent years, it is significant that the trend in total marital dissolutions has shown a less alarming picture; the rise in divorces is being offset by the continued decline in marriages dissolved by death. Typhoid fever, tuberculosis and the hazards of childbirth, "the great homebreakers of the past," have been virtually eliminated by recent advances in medical science, sanitation and public health. Another speaker pointed out that, on the basis of census data, the average male worker of 20 years of age in 1940 had a life expectancy of 46.8 years and a labor force life expectancy of 41.4 years.

Included in the second section, Tools for Demographic Research, is a brief explanation of the sampling method used in the current population surveys of the Bureau of the Census. In this monthly "miniature census," about 25,000 households in 68 counties are interviewed for information on a variety of subjects. The papers also concerned the various recent proposals for modifying the net reproduction rate and the use of census tracts and divisions in the recording of the 1950 census data in the state of Washington. Soil resources and potential food supply and their effects on population increases are discussed in the papers in the section on Resources for the World's People. One speaker assures us that "we need have no fear in this country of declining levels of food consumption because of past abuse of our lands—not even, as will appear presently, after allowing for all the exports other nations will buy from us" (page 54). Another warns that ". . . even if we could increase food production for the next few decades twice as fast as appears probable we cannot be at all certain that when the end of such a period arrived most men would be any better off than they now are, unless, in the meantime, we had learned how to control our own conduct as regards the rate of reproduction" (page 92).

In the section Value Systems and Human Fertility are included analyses of the reproductive mores of the Asian peasants and of the people of the Middle Ages which attempt to show that fertility rates cannot be studied apart from the total cultures. In one paper it is pointed out how the Catholic value system influences the fertility aspects of behavior.

In discussions on the Future Course of Research in Fertility, a physician presents current medical thinking on the "physiologic aspects of the control of fertility" and the more important advances in this area. Other speakers pointed out the measures and methods to be used in future studies of fertility as well as some of the fields in which study is needed.

The American Family: A Factual Background. Report of Inter-Agency Committee on Background Materials. National Conference on Family Life, May 1948. Paper. Pp. 457. U. S. Government Printing Office, Washington, D. C., 1949.

The general purpose of the Conference on Family Life was to discover specific means by which the American family might be strengthened for the benefit of its individual members and society. This volume contains material on the basic family and population statistics, the family in the American economy, education, health, housing, legal status, income maintenance and social services to families.

The term "family," as revised by the Bureau of Census, is "A group of two or more persons living together and related by blood, marriage, or adoption; all persons residing together and related to each other are regarded as one family." Population and family trends, marriage and divorce rates, mortality statistics and migration statistics are among the many items covered in the first chapter. Chapter 2, The Family in the American Economy, discusses trends in the labor force participation, the number of workers per family and the number of women workers in the family. Recent changes in family income are treated in this volume, and the trends of consumer expenditures for various products are presented in the form of tables. Statistics on the relation between education and marriage were developed, such as education as it relates to family living. Trends in school attendance of children and shifts in distribution are treated at great length, with the inclusion of many tables presenting data by age and by states. Family health has been related to such factors as prenatal influences, infancy and childbirth, environmental sanitation, housing conditions, income and the receipt and costs of medical care. There are tables of the percentages of births in hospitals in each state, infant mortality by state and the number of children crippled by various diseases. The conditions and facilities of the housing of families are discussed in chapter 5, Housing for American Families. Also included in this chapter is information on the amount of overcrowding, size of households, impact of wars and trends toward rural, nonfarm areas. Estimates of needs of future housing have also been made. Chapter 6, Legal Status of the Family, discusses the property rights and powers of contract of husband and wife, the custody, control and earnings of minors, laws affecting the school attendance, annulments and divorce. Income maintenance programs regarding social insurance and public assistance are presented in chapter 7. Also discussed in this chapter are the family and child welfare services, as well as various other social services to families. Many tables are presented of mortality and natality statistics, family income and distribution of personal income, consumer expenditures, school enrolments, number of teachers in schools, dwelling units and various insurance plans. Most of the statistics are for the years 1945, 1946 and 1947, with some historical trend tables. This volume contains a wealth of knowledge about the various factors relating to the American family.

Elements of Medical Mycology. By Jacob Hyams Swartz, M.D., Assistant Professor of Dermatology, Harvard Medical School and Postgraduate School, Boston. In Collaboration with Ethel M. Rockwood, M.D., Dermatologist, Massachusetts General Hospital, Boston. Introduction by Fred D. Weidman, M.D., Professor of Dermatological Research, University of Pennsylvania, Philadelphia. Second edition. Cloth. $5.50. Pp. 249, with 138 illustrations. Grune & Stratton, Inc., 381 Fourth Ave., New York 16, 1949.

Problems of the pathognomy, diagnosis and therapy of fungus diseases are encountered daily by physicians; their resolution remains one of the engimas of modern medicine. Relatively few American textbooks have been published on the subject during the past two decades, and none adequately covers the field of mycology. With the advent of chemotherapeutic agents, including the antibiotics, increased interest in medical mycology has been manifested by physicians in the hope that cures of fungus diseases could be effected by those agents. With the exception of the sulfonamides and penicillin for the treatment of actinomycosis, none of those agents has proved to be effective against surface or systemic fungus infections. Therapy of the majority of these diseases has changed little throughout the years; cures of the systemic infections are comparatively rare.

This volume represents a handbook of medical mycology and will prove a valuable addition to the reference volumes on every physician's bookshelf and in clinical laboratory libraries. It is not a complete reference book but contains practical information on the pathogonomy, diagnosis and therapy of many pathogenic fungi. In many respects it supersedes the "Manual of Clinical Mycology," published in 1945 under the auspices of the National Research Council. The author, a disciple of Carroll W. Dodge, has followed the latter's classification of the fungi and has arranged the subject matter, including an excellent chart of the pathogenic fungi, according to fungus genera. The chapter on the diagnosis of fungus infections by specific procedures reflects the interest and practical experience of the author in the laboratory aspects of the subject.

Epidemiology in Country Practice. By William Norman Pickles, M.D., Medical Officer of Health, Aysgarth Rural District, Yorkshire. With a Preface by Major Greenwood, F.R.S., D.Sc., F.R.C.P., Professor of Epidemiology and Vital Statistics in the University of London. Re-issued 1949. Cloth. $2.50. Pp. 112, with illustrations. The Williams & Wilkins Company, Mount Royal & Guilford Aves., Baltimore 2, 1939.

This book was first published in May 1939, after which the demand for it was regular and continuous until April 1941, when the entire bound and sheet stock and the type were destroyed by enemy action. In response to numerous requests, the publishers had it entirely reset and republished in virtually the same form as when first issued. The reader who expects to find epidemiological data on large numbers of cases will be disappointed. It might well be called an essay on epidemiology in country practice. It includes several papers published by the author from time to time in medical journals. It is intended for the general practitioner and illustrates well that there is a vast amount of epidemiological information to be gleaned from clinical observation in one's own practice.

Major Greenwood says in the preface, "Budd was one of the last of those physicians who did their own epidemiology, and were not content to sow for others to reap. We have, indeed, had to wait a long time for a second Budd but (in Dr. Pickles) I think we have found one." The author has written as the local health officer and general practitioner in an isolated rural community. His close association with the people and his inti-

mate knowledge of them gave him the unique opportunity to make and record firsthand observations on the entire course of diseases as related both to the individual and to the community. This is particularly true with regard to unusual opportunities to determine definitely the incubation period in many patients. The lack of large numbers of observations is offset by the completeness and thoroughness of those made by the author in establishing his own epidemiology.

A practical common sense point of view is obvious. The opinions expressed as to management of communicable diseases, the relative value of hospitalization, quarantine, isolation and other procedures are as sound now as they were when they were written. The commoner communicable diseases are described as they occur in the author's practice. There are interesting chapters on epidemic catarrhal jaundice and epidemic pleurodynia (myalgia). In addition to the technical information the book contains, it has much of historical interest; and the wit, philosophy and common sense woven in make it pleasant and interesting reading. If it creates a desire in the general practitioner to study the course of communicable diseases in the patient and the community, as the author did, it will have served a good purpose. The paper and printing are good; there is a bibliography and a complete index.

Aus den Anfängen der Psychoanalyse: Briefe an Wilhelm Fliess, Abhandlungen und Notizen aus den Jahren 1887-1902. Von Sigm. Freud. Cloth. 30s. Pp. 477, with illustrations. Imago Publishing Co., Ltd., 10 Nottingham Place, London W.1, 1950.

This book contains selections from a correspondence between Sigmund Freud and the Berlin physician and biologist Wilhelm Fliess and some notes and manuscripts on the etiology of the neuroses, anxiety, melancholia and hysteria. The letters presented here are those which Freud addressed to Fliess. They were discovered in an antique book market together with other effects of Fliess. The letters which Fliess sent to Freud have not been found. Freud was between 31 and 46 years of age when these letters and manuscripts were written. This was the time when he first established himself as a specialist for nervous diseases. He discussed with his friend Fliess his plans, successes and failures. The letters contain not only those ideas which finally were elaborated into Freud's psychoanalytic theories but also the bypaths and false starts, thoughts and conclusions which he later rejected. Marie Bonaparte, Anna Freud and Ernst Kris arranged this material for publication. They selected 168 communications of a total of 284, giving emphasis to those which were concerned with the scientific investigations of the writer and those which throw light on the social and political conditions of the time. They are aware of the fact that Freud would not have published any of this material, for he never presented to the public anything that was not complete. They feel, however, that this material, which was saved from destruction by a lucky accident, throws new light on the development of the theory of psychoanalysis and that it will be of interest to those who are familiar with Freud's published works.

The Nutritional Improvement of Life. By Henry C. Sherman. Cloth. $3.75. Pp. 270. Columbia University Press, 2960 Broadway, New York 27, 1950.

Dr. Sherman has drawn on his lifetime of writing and research in the field of nutrition to present a comprehensive review of the advances made in the science of nutrition up to the middle of the twentieth century. The language used is simple and nontechnical. The significance of the discoveries of nutritional research is presented rather than the technics employed. As Dr. Sherman remarks in the preface, "Nutrition is everyone's adventure. This book brings out the human implications. It differs from others in its field—and from scientific books generally—in that it deals less with how the advances of yesterday were made, and more with what they can mean for today and tomorrow."

The first part of the book follows the progress of nutrition throughout the half century of its recognition as a distinct science. The latter part of the book contains an excellent discussion of current nutritional developments and their implications for the betterment of life. An appendix contains a summary of the 1946 World Food Survey of the United Nations' Food and Agriculture Organization. A second appendix gives records of actual meals which illustrate how the present day knowledge of nutrition can be applied to an average twentieth century diet. A carefully selected bibliography which includes abstract as well as original references concludes the book. Anyone who has an interest in the science of nutrition will find this book of value. Its nontechnical language will appeal particularly to laymen and students. It is an excellent book for the physician to recommend to those of his patients who desire an easily read reference on nutrition and its effect on human life.

The Physiology and Pathology of Exposure to Stress: A Treatise Based on the Concepts of the General-Adaptation-Syndrome and the Diseases of Adaptation. By Hans Selye, M.D., Ph.D., D.Sc., Professor and Director of the Institut de médecine et de chirurgie expérimentales, Université de Montréal. Preliminary edition. Paper. $14. Pp. 792, with illustrations; 263R. Acta Endocrinologica, Inc., 5465 Decarie Blvd., Montreal 29, 1950.

The author has played a primary role in the development of the theory with which this impressive volume deals. In this carefully developed treatise, the principal facts and theories on which the general adaptation syndrome concept is based are thoroughly discussed. Definitions of terminology used are outlined, and the various alarming stimuli or factors which elicit the syndrome are described. Whether one agrees with the concept of the syndrome or not, work with pituitary adrenocorticotropic hormone (ACTH) and cortisone has lent support to many of the basic concepts on which its theory depends.

If future events prove that this concept is correct, it will prove to be one of the significant medical advances in understanding the nature of disease of this century. One can carp at the somewhat rigid division of the adrenal steroids into mineralocorticoids, glucocorticoids, medulloids, lipocorticoids and others, since many of the steroids have been shown to have significant actions in several of these fields. However, the general stature of Selye's work requires no defense. Every serious student of internal medicine and endocrinology is almost constrained to familiarize himself with this textbook. The bibliography is most thorough.

The Physiology of Work and Play: A Textbook in Muscular Activity. By Sarah R. Riedman. Cloth. $4.90. Pp. 584, with 158 illustrations by Ida Scheib. The Dryden Press, Inc., 386 Fourth Ave., New York 16, 1950.

As stated in the preface, this volume is primarily a textbook on the physiology of muscular activity written for undergraduates in physical education, physical therapy and recreation. The well-organized table of contents indicates that the book is divided into five parts. Part 1 considers muscle physiology, fatigue and the nervous control of muscular activity. Part 2 discusses cardiovascular-respiratory functions in relation to exercise. Part 3 is concerned with the internal environment of the body and changes occurring in the blood, tissue fluid and lymph as a result of skeletal muscle activity. Part 4 discusses skeletal muscle activity and work under such limiting environmental conditions as unusual barometric pressures and extremes of temperature and humidity, as well as under conditions of modern industry. Part 5 contains information of interest to the practicing physician with reference to convalescence and reconditioning, therapeutic exercises, physical fitness, somatotypes and psychosomatic interrelations of the nervous and skeletal muscle systems.

Since the scientific background of physical education students is not uniform, the author includes pertinent material on gross anatomy, histology and chemistry. The basic and applied physiology of exercise are well presented, but in some instances accuracy has been sacrificed for brevity and simplicity. Thus it would be more accurate to say that for all practical purposes cardiac muscle cannot be tetanized rather than that "cardiac muscle can not be tetanized at all" (page 32); and that immobilization of a limb decreases rather than "prevents the flow of impulses both to and from a muscle" (page 52). The cerebellum aids importantly in postural reflex mechanisms but is not a center for postural reflexes (page 195). Contrary to the information on page 212, atropine decreases sweat secretion. The cardiac output values quoted on page 270 and obtained by the acetylene method have in recent years been shown by the cardiac

catheterization technic to be too low. Contrary to the statement on page 371, the capillary wall is only relatively impermeable to the plasma proteins. There are also a few confusing typographic errors, such as "the R.Q. was 9 and 9.5" (page 85), and "running increased the f.f.f. [flicker fusion frequency] by 80 to 90 per cent" (page 156).

The style is clear; the illustrations are satisfactory, and the index is adequate. A good summary and pertinent reference list are included at the end of each chapter. The format of the book is in keeping with its list price. This volume is recommended for students of physical education, physical therapy and recreation, as well as others interested in this field of human physiology. Physicians will find part 5 of value.

Professional Nursing: Trends and Adjustments. By Eugenia Kennedy Spalding, R.N., M.A., Professor of Nursing Education, Indiana University, Bloomington, Ind. Fourth edition. Cloth. $4. Pp. 536, with 29 illustrations. J. B. Lippincott Company, 227-231 S. 6th St., Philadelphia 5; Aldine House, 10-13 Bedford St., London, W.C.2; 2083 Guy St., Montreal, 1950.

This book has been extensively revised and enlarged to give a fuller understanding of the many social, economic, professional and other factors that are directly related to the nursing field. First, there is an introductory section describing the technic of collecting, evaluating and organizing source material essential in the study of nursing problems and methods of professional readjustment. In unit 1, the Social and Professional Outlook of the Graduate Nurse, the discussion centers on nursing as a profession, recent advances and current problems that may affect the future of nursing. The succeeding section contains a survey of occupational opportunities for professional nurses, information on nurses in public service, selection of work, continuation of education and the procedure for obtaining employment and resigning from a position. Unit 3 presents up-to-date information on the activities of professional organizations in the nursing field and also discusses nursing and related legislation, public relations in nursing and the organizational principles and practices which aid in professional activities. The concluding section concerns legal relations, problems of economic security and professional relations with physicians, patients and their families and other members of the nursing staff. Suggestions are also made with reference to mode of living, leisure activities, personal appearance, gracious manners and tact.

This book is written primarily for the professional nurse and offers a wealth of information on nursing organization, activities and relations that will be helpful in making readjustments to individual problems. Methods of procedure are fully described in each chapter, and there are an extensive bibliography and suggested references.

The Theory of Camping: An Introduction to Camping in Education. By Frank L. Irwin, Ed.D. Cloth. $2.50. Pp. 173. A. S. Barnes and Company, 101 Fifth Ave., New York 3, 1950.

Different from many books on the subject, this volume is concerned chiefly with the educational aspects of camping and with ways of integrating the objectives of camping with the general purposes of education in America. While the methods through which camping can help to achieve educational goals are outlined, as the title indicates, the book is in no sense merely a manual of camping activities. Instead, it seeks to present the basic principles of good camping, on which specific programs may be built in particular situations. Organized camping is defined as an educational enterprise providing children with an opportunity to live, work and play in a group situation, to obtain experience and insight into many of the basic processes of life and to receive guidance from a mature counselor who influences the camper all during the day over an extended period of time. After tracing the development of camping in the United States, the author shows how a properly organized and conducted program can contribute to self reliance, economic efficiency and civic responsibility and at the same time provide unusual opportunity for experience and training in human relations. The importance of understanding the individual camper and meeting his personal needs within a situation that inherently stresses group living is emphasized. The camp program is then considered, with stress on the vital role that good counseling and administration play in providing a worth while schedule of activities. A description of day camps and public school camping, together with up-to-date bibliographies, add to the usefulness of the volume. Physicians concerned in any way with camping will be particularly interested in the section on health and safety which, although brief, provides satisfactory coverage of the health service aspects of camping.

The American Red Cross: A History. By Foster Rhea Dulles. Cloth. $5. Pp. 554. Harper & Brothers, 49 E. 33rd St., New York 16, 1950.

Written with an approach that shows no bias, this historical review presents the story of the American Red Cross ably and completely. It is essentially a condensation and extraction of a series of monographs prepared by a special division set up within the organization. The author also had access to official records and states specifically in his preface that no restrictions or pressures were applied to influence the way in which those were used.

Personalities are always interesting subject matter, and the author shows special skill in the presentations scattered throughout the book of important personages who have guided the Red Cross over its lifetime of more than 70 years. Perhaps the most unusual of these was the founder, Clara Barton. Although growth of the Red Cross might now seem to have been the most natural and inevitable thing in the world, actually it was a struggle that called for perseverance and faith on the part of those associated with its early beginnings and the "growing pains" from which it suffered at intervals. These are described with candor in three different chapters, one on controversy and reorganization, another on criticism and reform and the third on the Red Cross and the New Deal.

In addition to the 30 chapters describing the Red Cross, its services in war and in peace, international operations, volunteer activities, special features, such as the blood donor program and aid to prisoners of war, a final chapter lists in specific detail the source material on which the author was able to draw. As the author states, this is the first complete history of the Red Cross. It is a thoroughgoing piece of work that should be of widespread interest for persons in all levels of society.

Developments in Diphtheria Prophylaxis. By Lewis B. Holt, M.Sc. Cloth. 42s. Pp. 181, with illustrations. William Heinemann Medical Books, Ltd., 99 Great Russell St., London W.C.1, 1950.

In 1926, Glenny and others demonstrated that the antigenic power of alum-precipitated diphtheria toxoid was greater than that of the plain or nonprecipitated product. The newer preparation proved too irritating for administration to children, but it was later found that careful washing of the precipitate provided a product which could be used for human immunization.

Alum-precipitated diphtheria toxoids often vary in potency even under regulated and well controlled methods of production. These variations, with their attendant problems of adequate diphtheria prophylaxis, prompted the author's search for a reliable and accurately reproducible prophylactic of high potency and stability. The work includes the description of a method for preparation of such a product and of the antigen and the alum precipitate.

Data are presented which reflect the effect of p_H, temperature, formalin concentration, minerals, types of aluminum salt and other variables on the quality of the toxoid prepared.

Considerable space is devoted to a critical review of the current theory, postulated by Glenny, that the increased antigenic efficiency of alum toxoid is due to slow absorption and elimination. An alternative explanation, supported by experimental data, is offered for the greater physiological activity of the precipitated toxoids as compared with their parent formol toxoids. It is postulated that the optimum amount of alum is of far greater importance than the amount of antigen, since when the amount of mineral carrier (alum) is increased, the antigen is efficiently distributed among a large number of antibody-producing cells. The author suggests the possibility of a standard or reference diphtheria prophylactic, based on the "purified toxoid, aluminum-phosphate-precipitated" preparation he describes. No reference standard for these products is presently recognized by government agencies in England or the United States.

Textbook of Anatomy and Physiology. By Catherine Parker Anthony, B.A., R.N., Instructor of Anatomy and Physiology, Lutheran Hospital, Cleveland, Ohio. Third edition. Cloth. $4. Pp. 614, with 208 illustrations. The C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, 1950.

This textbook is designed for use in nurses training schools where the two subjects anatomy and physiology are combined in a single course; it is also suitable for reference in high schools and for use in college courses. The style and arrangement are intended to facilitate teaching, and each chapter is provided with an introductory outline, a unit vocabulary, a concluding outline-summary and review questions. In addition, there are useful tables, a wealth of attractive illustrations and a good index.

Attention should be called to a medical superstition innocently perpetuated by the author on page 442, where it is stated that a person whose frenum linguae is "too short for freedom of tongue movements" is said to be tongue-tied and to have faulty speech. No speech defect of this sort is recognized in modern textbooks on speech correction; on the contrary, cutting of the frenum in the newborn may be followed by deformities that do entail speech defects. This was pointed out by McEnery and Gaines in 1941. On page 517 the author advises that in babies with undescended testes measures should be taken to bring the testes down into the scrotum. This recommendation should be replaced by the physiological facts noted by Drake in 1934, and by others as well, who found an incidence of more than 5 per cent of undescended testes in otherwise normal boys at birth, and who showed that in the overwhelming majority of these cases spontaneous postnatal descent occurred, sometimes as late as the age of 18 years. Drake concluded that the only case that should be considered a surgical problem is the bilateral one persisting to the age of 14 or the unilateral case with complications. It is hoped that these two errors, both capable of doing incalculable harm, will soon be eradicated from medical literature and will be corrected in future editions of this otherwise commendable book.

American Red Cross Home Nursing Textbook. Prepared under the Supervision of Nursing Services, American Red Cross. [Sixth revision.] Cloth. $1. Pp. 235, with illustrations. The Blakiston Company (Division of Doubleday & Company, Inc.), 1012 Walnut St., Philadelphia 5, 1950.

This book is an informative and helpful presentation of home nursing procedures. The instruction given is based on the assumption that the patient's treatments, other than emergency first aid, are ordered by a physician and that the general nursing care is under a physician's supervision or that of a professional registered nurse. The book is prepared primarily as a textbook for those who take the Red Cross home nursing course, but it will be helpful to others. It includes information on how to meet simple home emergencies, how to recognize some of the early signs of illness, how to provide simple nursing care for the sick and injured at home and how to help keep the family well. There are detailed instructions for carrying out many home nursing procedures. Selected additional references for those who wish to study further are mentioned. This textbook will be welcomed by its old acquaintances and the newer ones that it will make.

William Withering of Birmingham, M.D., F.R.S., F.L.S. By T. Whitmore Peck, M.P.S., and K. Douglas Wilkinson, O.B.E., M.D., F.R.C.P. Cloth. $4.50. Pp. 239, with illustrations. The Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1950.

This account of Dr. Withering's life and enterprises is no mere biography, in the conventional sense, but is more exactly a work of the heart. It is as though the authors desired to build a memorial to the man who had been a source of inspiration to them; and in so doing to instil in others a measure of the zeal they had derived from a study of his life. This gives one the feeling that the book is primarily oriented toward the student.

The authors have succeeded in compiling an interesting and moving account of the maturation and full realization of a man of genius, an account well documented and at the same time free from pedagogy. The book is replete with the letters, notes and case histories compiled by the famous physician of Birmingham, and the authors have chosen the best course—they let the man speak for himself—for William Withering was a man of vision, as a quote from "An Account of the Foxglove" will testify: "After all, in spite of opinion, prejudice, or error, Time will fix the real value upon this discovery (digitalis) and determine whether I have imposed upon myself and others, or contributed to the benefit of science and mankind."

The book contains a measure of interest for the layman, there being an absorbing description of the social milieu in which Dr. Withering lived and the relation of the doctor to his contemporaries. Throughout, this work is pervaded by the character of Dr. Withering, a man at once a great scientist, a good physician intimately concerned with the welfare of his patients and an active citizen of the community—a man who felt and shouldered the responsibilities entailed in being a physician.

Taxes and Economic Incentives. By Lewis H. Kimmel. Cloth. $2.50. Pp. 217. The Brookings Institution, 722 Jackson Place, N.W., Washington 6, D. C., 1950.

Realizing that the heavy revenues needed to finance greatly increased governmental expenditures can only be raised in an expanding economy, the author has prepared an analysis and appraisal of the principal taxes now employed from the standpoint of economic incentives. His study opens with a general discussion of taxable capacity in a free enterprise economy, which he defines as "the capacity to raise revenues without extreme interference with productive activity and the operation of the economy." The principal determinants of taxable capacity —the volume and composition of national income, the nature of governmental expenditures, the available methods of taxation and the reactions of people to tax burdens—are reviewed. Major emphasis is placed on the reactions of taxpayers. The four major taxes—income, sales and excise, property and payroll—are each examined in relation to four principal incentives essential to a dynamic and growing economy. These are the incentives to establish new businesses, for existing businesses to expand, to invest and to work. A discussion of incidence and shifting is presented in respect to each type of tax. Direct information on the reactions of the business community to specific taxes, which was obtained from a questionnaire sent to 1,000 manufacturing corporations, is also included.

This study indicates that the corporate income tax and the personal income tax are most detrimental to economic incentives. Decisions relating to the expansion of existing enterprises, particularly in the case of the small and moderate-sized firm, are considerably influenced by the corporate income tax, while the personal income tax has its greatest effect on the volume of savings available for investment. The incentive to work and the incentive to establish new enterprises seem to be influenced more by other factors than by taxes. Apparently, sales and excise taxes and property taxes have less effect on economic incentives than is generally believed. While the present rate of payroll taxes has not been found to be burdensome, an increase in this rate might have serious repercussions. Most important among the author's recommendations for an effective tax policy is a proposal for the coordination of the personal and corporate income taxes and the substantial reduction of the corporate income tax as such. His proposal is aimed at removing the present tax deterrents to business expansion without appreciably reducing any tax source. He stresses the importance of a balanced system of diversified taxes. With the events of the past few months and the necessity for even greater governmental expenditures, this book is particularly timely.

The Hormones: Physiology, Chemistry and Applications. Volume II. Edited by Gregory Pincus and Kenneth V. Thimann. Cloth. $12.50. Pp. 782, with illustrations. Academic Press, Inc., Publishers, 125 E. 23rd St., New York 10, 1950.

This volume includes the bulk of studies in animal physiology and bioassay procedures relevant to endocrinology. Clinical endocrinology is relegated to a single chapter of 40 pages which, while well handled, of necessity must be sketchy. The chapters on physiology and chemistry are valuable sources of experimental evidence for present day theories of endocrine function. The bibliography is comprehensive. The series will prove most valuable to the serious student of endocrinology and those interested in experimentation in this field. The intent of the editors is a complete presentation of the subject at the research level. They have succeeded remarkably well in attaining this goal.

QUERIES AND MINOR NOTES

The answers here published have been prepared by competent authorities. They do not, however, represent the opinions of any official bodies unless specifically stated in the reply. Anonymous communications and queries on postal cards will not be noticed. Every letter must contain the writer's name and address, but these will be omitted on request.

IMMUNIZATION OF DIPHTHERIA CONTACTS

To the Editor:—What is the accepted opinion regarding the use of passive immunization concurrently with active immunization in diphtheria contacts? Apparently those who object to active immunization being started at the same time that passive immunity is induced believe that one interferes with the other. Harold W. Conran, M.D., Suva, Fiji.

ANSWER.—It is generally accepted that active immunization of susceptible contacts of diphtheria cases is practical and effective when the first of two or three doses of antigen is given simultaneously with a prophylactic serum antitoxin. The empirical belief that the resulting protection from toxoid is neutralized to some extent by the passively acquired antitoxin and that the resulting protection from the passively acquired antitoxin is neutralized to a small extent by the toxoid has been confirmed by animal and human studies. However, the amount of interference of one by the other appears to be so small as to be negligible when optimum procedures are used.

The protection conferred by toxoid in animals and humans depends not only on the amount of toxoid used, the number of doses and the interval between doses but on the prior experience of the patient with diphtheria infection or immunization. Persons who have had such prior experience have their immunity mechanism sensitized so that they respond within a few days to a single small dose of toxoid and seldom require antitoxin. Persons not so sensitized need basic immunization, which requires much longer to develop. They require an effective primary stimulus before they can mobilize adequate amounts of antitoxin in the circulating blood. Such persons are of chief concern in considering the probable effectiveness of simultaneous active and passive immunizations. In such persons the primary stimulus induced by the first dose of toxoid is delayed and inhibited by simultaneous administration of prophylactic antitoxin. The protection following the second dose is increased either when the amount of toxoid in the first dose is increased or when the amount of antitoxin is decreased. Alum-precipitated toxoids give better response than plain toxoids, and alum-precipitated toxoids are more effective when given with a four instead of a two week interval between doses.

Available data indicate that during the eight week period following the second of two doses of alum-precipitated toxoid, which has been given with a four week interval to completely susceptible persons, those who receive 500 to 1,000 units of antitoxin at the time of the first dose are not as well protected as those receiving no antitoxin. However, after 14 weeks the protection in those receiving antitoxin is almost as good as in those receiving no antitoxin (Downie, A. W., and others, *J. Hyg.* 46:34 [March] 1948). The final slight difference in protection is of little consequence but can be obviated if one gives a third dose of toxoid or increases the interval between doses to six weeks. It is important that susceptible diphtheria contacts be kept under careful observation during the period when the passive immunity is low and the active immunity has not fully developed.

SENSITIVITY TO EMBALMING FLUID

To the Editor:—A mortician has a skin sensitivity to embalming fluid with a formaldehyde base. Is there an embalming fluid with other constituents available? Can the man be desensitized to formaldehyde?

L. R. Evans, M.D., Laramie, Wyo.

ANSWER.—The skin of many persons becomes inflamed by contact with formaldehyde fumes or solutions. Generally the skin of such persons is sensitive also to other substances or solutions, such as soaps. One so constituted must make adjustment to prevent or to minimize contact with these chemicals or substances. Morticians are supplied by manufacturers with embalming solutions that must comply in chemical content with state or federal regulations. Solutions with low formaldehyde content, or perhaps with no formaldehyde, are now available. Inquiry about these may be directed to the Champion Chemical Company, Springfield, Ohio; Dodge Chemical Company, Boston; Undertakers Supply Company, Westport, Conn., or Undertakers Supply Company, Chicago. There is no known procedure for desensitization against formaldehyde preparations.

EXCESSIVE PERSPIRATION FOLLOWING SYMPATHECTOMY

To the Editor:—A man aged 50 had a bilateral sympathectomy eight years ago for relief of Raynaud's disease of the fingers. Since then he has had excessive perspiration of the entire trunk of the body. This is a source of great embarrassment and retards his advancement in his company. Are there any drugs that might offer him relief?

W. F. Francka, M.D., Hannibal, Mo.

ANSWER.—Excessive sweating in hot weather is a common sequence of partial sympathectomy, because sweating is inhibited over the sympathectomized part of the body and the limited number of remaining functioning sweat glands have to work overtime in aiding dissipation of heat through evaporation. Whether this mechanism is important in this case cannot be determined, because the extent of the sympathectomy and circumstances of sweating are not stated. It is probable that the basic autonomic disturbance responsible for the original Raynaud's syndrome plays a role here. Excessive sweating, particularly of the axillas, palms and soles, commonly accompanies Raynaud's disease, and emotional stress seems to be an important factor in both the sweating and vasoconstriction of this disease. Furthermore, as Kuno has shown, mental and emotional stress influences sweat gland activity not only on the palms, soles and axillas but on the trunk. That emotional factors may be a contributory factor in this case is suggested by the fact that the patient allows the sweating to embarrass him socially and to retard his advancement in his company.

Drugs which block sweat gland activity are contraindicated where sweating is necessary for heat dissipation, as the body temperature would rise. Furthermore, the newer drugs which block the autonomic nervous system have side-effects and other disadvantages which preclude their continued use. If high environmental temperature is an important contributing factor, the installation of air conditioning or other cooling devices in the office and/or home should be considered. In any case, treatment should be directed toward getting the patient to accept the fact that sweating need not block his social and business progress.

RH ISOSENSITIZATION BY PREGNANCY

To the Editor:—A 25 year old quadrigravida is Rh negative, and her husband is Rh positive. The first child is six years old and well. The second child was delivered at eight months, lived six days and died. The third baby was delivered stillborn at six months. The patient is now three months pregnant. The result of the Wassermann test is negative. There is no history of venereal disease. How can I help this patient?

Alfred H. Hathcock, M.D., Fayetteville, Ark.

ANSWER.—The clinical story is strongly suggestive of Rh isosensitization by pregnancy, but the actual diagnosis depends on the results of tests for Rh sensitization. Blood specimens should be taken from the expectant mother and father and from the child and sent to a laboratory specializing in Rh tests. This laboratory will verify the Rh type of the husband and the wife and determine the Rh type of the living child. In addition, the laboratory will test the mother's serum in order to determine whether she is sensitized to the Rh factor. There are at least three possible results:

1. The tests may reveal that the original typing of the patient is incorrect and that she is actually Rh positive, or they may show that, although the patient is Rh negative, she is not sensitized to the Rh factor. In that case Rh sensitization could not be the cause of the neonatal death and the stillbirth, and some other explanation would have to be sought. The prognosis for the present pregnancy would then depend on the explanation found.

2. A stronger likelihood is that the laboratory tests would confirm the previous report that the patient is Rh negative and her husband Rh positive and, in addition, would show that the patient is sensitized to the Rh factor. Such results would support the surmise that the second baby probably died from erythroblastosis and that the stillbirth was also probably due to Rh sensitization. The prognosis for further pregnancies would then depend on the Rh type of the fetus. If the fetus is Rh positive, another stillbirth would be likely; if the fetus

is Rh negative, it would not be harmed by the maternal Rh antibodies. It would be helpful in this connection to determine whether the husband is homozygous or heterozygous for the Rh factor. A presumptive diagnosis as to genotype could be made by Rh-Hr typing of the husband. For example, if the husband belongs to any of the types Rh_1Rh_2, Rh_1Rh_1 or Rh_2Rh_2, he is probably homozygous for the Rh$_0$ factor, but if he belongs to type Rh_1rh or Rh_2rh he is probably heterozygous for the Rh$_0$ factor. It might be possible for one to determine the husband's genotype more exactly by typing his parents, if they are available, and also from the Rh type of the living child. Where the expectant mother is strongly sensitized to the Rh factor and the husband is homozygous for the Rh factor, a therapeutic abortion may be indicated, provided the pregnancy is not too far advanced. The abortion would be indicated not only because such a pregnancy would be futile but because it involves increased hazards for the mother, since toxemia and severe postpartum hemorrhage are not infrequently associated with hydropic stillbirths. In the present case, in which the pregnancy is already far advanced, the only recourse is to handle the problem as conservatively as possible.

3. A third possibility is that the neonatal death and stillbirth were not due to erythroblastosis but that now the patient has become sensitized to the Rh factor as an additional complication. In such an event attention should be focused primarily on the problem of Rh sensitization. If the tests indicate that the fetus in utero is almost surely Rh positive, it might be possible to save the baby by delivering it prematurely and treating it without delay by exchange transfusion. If, however, there is a possibility that the fetus might be Rh negative, the pregnancy should be permitted to go to term.

UNDESCENDED TESTICLE

To the Editor:—A 12 year old boy has bilateral indirect inguinal hernia, a small hydrocele on the left and an undescended testicle on the right, which could not be felt in the canal. He also has a large umbilical hernia. I gave him a preparation of chorionic gonadotropin (5,000 units) without success. I planned to repeat the course, but the child never returned. His mother recently told me that he is now taking tablets. What could these be? At what age should treatment with gonadotropins be started? If they do not correct the cryptorchidism, is a Torek operation indicated? Does this operation make a testicle capable of spermatogenesis?

Erwan L. Levine, M.D., Vandalia, Mo.

ANSWER.—Frequently a hernia cannot be felt in association with an undescended testis, although it is surgically present in a high percentage of cases. In the case of this 12 year old boy, it is generally the belief that 30,000 units of anterior pituitary-like hormone constitutes sufficient total dosage, given two or three times a week, 500 units per dose. This course should bring the testis down in about 25 per cent of patients at this age. If the boy is taking methyl testosterone orally, no effect should be expected. One must not forget that a fairly high percentage of undescended testes descend during puberty, from about 12 to 16 years. If given before the age of puberty, gonadotropins should hardly be expected to effect descent of the testis. These substances will hasten puberty in boys near that age, at 10 or 11 years. Furthermore, gonadotropic hormones will cause descent only in boys whose testes would normally descend at puberty. A course of gonadotropic substances at 10 years of age may prevent surgical correction. If descent does not occur, operation is indicated, with either the Torek or elastic traction suture method. Spermatogenesis depends in large measure on careful preservation of the internal spermatic vessels.

DIETHYLSTILBESTROL IN PREGNANCY COMPLICATIONS

To the Editor:—I would appreciate information on the effects of diethylstilbestrol. What quantity can safely be taken in any given period or through pregnancy?

Paul M. Egel, M.D., Chicago.

ANSWER.—Diethylstilbestrol is a synthetic estrogenic drug and has the properties of all estrogens. Its use in the treatment of the menopause and in other conditions associated with ovarian failure is not complicated by untoward symptoms other than nausea for a few days after the institution of treatment in about 5 or 10 per cent of patients. It has been recommended for the prevention and treatment of some pregnancy complications, such as habitual abortion, diabetes and the toxemias. Graduated amounts of this drug are administered, beginning with 5 mg. daily and increasing to 125 mg. at 36 weeks' gestation. The efficacy of this therapy in the prevention and treatment of these pregnancy complications has not been proved; such proof awaits well controlled clinical experiments. There is little evidence that these amounts of diethylstilbestrol are harmful to the mother or the baby. Women can tolerate huge amounts of this drug during pregnancy without the occasional nausea induced by even small amounts in nonpregnant persons.

POTT'S DISEASE

To the Editor:—I have been using streptomycin and paraaminosalicylic acid in a case of tuberculosis of the last lumbar vertebrae (Pott's disease). The patient is 25 years of age. The patient's general condition is satisfactory and there is no deformity of the spine. What are the recommended average doses, duration of treatment and prognosis?

Juan José Lahuerta, M.D., Corella (Navarra), Spain.

ANSWER.—There are many different possibilities of dosage for the patient mentioned. Since bone lesions are rather slow to respond, the dosage used has been higher than that for pulmonary lesions. At least 1 Gm. of streptomycin, or 1.5 Gm. of dyhydrostreptomycin, should be given for 60 to 90 days. Because the bacilli may become resistant, the tendency now is to space the dosage every other day, or even every third day, and give 10 to 15 Gm. of paraaminosalicylic acid for four months or more. The paraaminosalicylic acid must be given in liquid form, 3 to 4 Gm. four times a day, near meal time, as a full stomach helps to prevent nausea. If nausea develops and persists, it is sometimes necessary that treatment be stopped for a few days. Usually the patient tolerates the drug on the second attempt.

RECTAL TEMPERATURE OF INFANTS

To the Editor:—What is the normal rectal temperature of an infant?

J. J. Johnson, M.D., Las Vegas, N. Mex.

ANSWER.—There is probably no "normal" rectal temperature for infants of 1 to 12 months but rather variable temperatures within the boundaries of normal. If the bulb of the rectal thermometer is inserted 5 cm. into the rectum, a higher temperature will be registered than if it is inserted only 3 cm. In the newborn the heat-regulating system is unstable. The temperature curves may show a considerable daily variation, which may be due to bodily movements, ingestion of food and the external temperature, all of which may cause a rise or fall of rectal temperature readings. The less protected the baby, or the cooler the room, the lower the temperature may be. Premature babies, of course, show the most pronounced variation in temperatures. It has been noted that bodily exercise may increase rectal temperature readings in normal infants; restlessness and crying may also cause such a temperature rise. A certain group of children show a constant rectal temperature of somewhat higher readings than the normal average; these infants are often members of neurotic families. Oscillations in rectal temperature are so universal that they should be considered normal manifestations based on a somewhat unstable heat-regulating mechanism in young infants.

MIXED MATINGS

To the Editor:—The maternal grandparents of a young married woman are white. Her mother is also white, as are her maternal aunts and uncles. Her paternal grandfather is a Negro, his parents having both been Negroes. Her paternal grandmother is light in color, one of her parents having been a Negro, the other white. The young woman's father is light in color; two of his sisters are colored. She herself is white and is married to a white man whose ancestors were all white. Will the offspring of this union result in white or Negro children?

M.D., New York.

ANSWER.—In a comprehensive study of mixed matings in Jamaica, British West Indies, Davenport (Heredity of Skin Color in Negro-White Crosses, Publication 188, Washington, D. C., Carnegie Institution of Washington, 1913) found that in 22 matings similar to that of the young woman's father, namely, of light-colored fathers having one of four possible genotypic factors for skin blackness with white mothers having no factors for black, or light-colored mothers with white fathers, there were 56 children of the same color of the white parents, 80 children of the same color as the colored parents and 1 child darker than the colored parents. Presumably, the young woman is of the genotype similar to the above group of children having no factor for black (the Caucasian type) and cannot, therefore, contribute a factor for black to her offspring; neither can her mate, who is of a similar genotype. Davenport investigated the question of dark children being born to a pure-bred white married to a white extracted by mendelian segregation of alleles in mixed matings of progenitors. He found that the idea of "reversion to black" was mythical.

DIAGNOSIS OF PREGNANCY

To the Editor:—I would like to know what the present status is of the skin test for the diagnosis of pregnancy.

E. S. Olson, M.D., Racine, Wis.

ANSWER.—There is no reliable skin test for the diagnosis of pregnancy, certainly none which can compare in reliability with the Aschheim-Zondek, Friedman, frog and many other tests.

ULCERS IN MOUTH AND THROAT

To the Editor:—A widower, aged 58, gave a history of ulcerations of the entire buccal cavity and throat for five months. On his first visit, he was so weak he was brought in with the help of the family. He said that he had not eaten anything for three weeks, having lived entirely on water, coffee and tea. I gave him livibron® (contains liver concentrate, thiamine hydrochloride, riboflavin, ferrous sulfate and manganese citrate), thiamine hydrochloride, vitamin B complex in large doses hypodermically and penicillin in sesame oil, 2 cc. daily. He has received these four drugs daily for 30 days. I also vaccinated him against smallpox, with a resultant "take." Since then he has been revaccinated twice without a "take." During the past month he has received typhoid vaccine, up to 3 cc., intramuscularly, which resulted in fever for periods of three or four days. Other medicaments given in full dosage include aureomycin hydrochloride capsules and troches and chloramphenicol. Phenindamine (thephorin®) was tried for five days. During the past three weeks he has received three roentgen ray treatments, consisting of 300 roentgen units, with 90 kv., 5 ma., at 8 inches distance, without additional filtration, given over a period of about one to one and one-fourth minutes. With the above therapy, he has gained 12 pounds (5.4 Kg.) and has been able to eat soft bland foods. The patient's teeth were extracted several years ago, but he does not use dentures. He does not smoke or chew tobacco. He has mild thrombophlebitis and recently had a small varicose ulcer of the leg, which cleared up. He has general arteriosclerosis with some varicose veins and, I suspect, mild cirrhosis of the liver. His buccal cavity, tongue and throat are still ulcerated, and the condition appears to remain unchanged. Is there any other therapy that might help the patient? Has he been overtreated?

H. W. Stevens, M.D., Wilson, N. C.

ANSWER.—The patient has received a great amount of treatment. The fact that he has improved in general suggests that the supportive therapy has been effective; the persistence of the oral changes indicates that therapy has not been specific. The future care of the patient should depend on diagnosis. If tuberculosis, stomatitis venenata and medicamentosa and other entities can be excluded, the diagnosis would seem to be either aphthous stomatitis or primary herpetic gingivostomatitis. These conditions are often not differentiated, though they should be because of their etiology and treatment. Blank, Burgoon, Coriell and Scott of Philadelphia have corrected previous misconceptions. Their studies on patients with recurrent aphthae failed to demonstrate the virus of herpes simplex; the virus was usually found in herpetic stomatitis. No specific herpes simplex antibodies were present in the aphthous cases. The cause of aphthous ulcers is unknown, and therapy is also uncertain. Recent reports indicate that aureomycin is of value, but it is possible that the condition was confused with herpes. The results from aureomycin were favorable in herpetic stomatitis. It is suggested that the diagnosis be made specific, if possible. The use of antibiotics and vaccine has perhaps been too brief, and further trial may be worth while, especially in the absence of immunologic studies. The use of smallpox vaccine should be continued for a series of eight vaccinations at 10 day intervals, whether or not there are "takes." Other methods of treatment have been mentioned in previous answers in this section (Feb. 7, June 12, July 10, Dec. 25, 1948; July 20, Sept. 24, Oct. 1, Dec. 24 and 31, 1949; March 25, 1950).

MYASTHENIA GRAVIS

To the Editor:—Please give what information you can about OMPA, which has been mentioned recently as a treatment for myasthenia gravis.

James W. Davis, M.D., Statesville, N. C.

ANSWER.—The designation OMPA denotes the phosphorus-containing insecticide octamethyl pyrophosphoramide, also known as pestox III. The compound was synthesized in Germany several years ago, and information regarding its pharmacology and toxicity may be found in the recent report of DuBois, Doull and Coon (*J. Pharmacol. & Exper. Therap.* **99**:376 [July] 1950). Inasmuch as OMPA is a strong anticholinesterase agent, it is likely to be of value in the treatment of myasthenia gravis. Preliminary clinical trials thus far have yielded promising results. At present the drug is available only for investigational use.

PENICILLIN, STREPTOMYCIN AND AUREOMYCIN

To the Editor:—Is there any practical means of administering aqueous procaine penicillin and streptomycin in the same syringe? Is there any evidence which indicates incompatibility between aureomycin given orally and penicillin given intramuscularly?

Berryman Green, M.D., Laguna Beach, Calif.

ANSWER.—Therapeutic forms of aqueous procaine penicillin and streptomycin are available for dispensing in the same syringe and from the same container. There is no evidence that there is incompatibility between aureomycin given orally and penicillin given intramuscularly.

ULTRAVIOLET RAYS IN PULMONARY TUBERCULOSIS

To the Editor:—I was in my third year at medical school when I contracted pulmonary tuberculosis. I am home now and have a 50 per cent uniform collapse of my right lung. The doctors feel I will be able to start school this September. Would it be detrimental to use an ultraviolet lamp for the purpose of getting a sun tan. I have asked a number of physicians, but they do not agree. If ultraviolet rays are used to treat tuberculosis of the skin and tuberculosis of the bone, would they be objectionable for sun tan in a person with controlled pulmonary tuberculosis?

Daniel McIntire, Lafayette, La.

ANSWER.—Ultraviolet rays for the treatment of pulmonary tuberculosis is risky because of the danger of overdosage. If treatment time is gradually increased—a minute or two for a week, then another minute or two for the next week, and so on—no harm will result. The risk, however, is out of proportion to the gain. There are many effects produced by ultraviolet rays, both locally and systemically. Some of these effects are known, some are not. There is an effect on the pigment of the skin, an inflammatory reaction where the blood cells are increased, and an increase in humoral substances, some of which are toxic. There is a wide difference between pulmonary tuberculosis and tuberculosis of the skin. Cutaneous tuberculosis is generally superficial and localized in the skin. Rarely does it spread beyond the skin. A lesion can be treated without much risk of spreading. In lung lesions the toxic agents in large dosage may cause a break in the cellular defense of the soft lung lesion, resulting in a spread to other parts of the lung or body. The effect is like that of any toxic agent, including burns.

FEVER THERAPY IN ASTHMA

To the Editor:—Please give information on fever therapy in cases of asthma.

M.D., Pennsylvania.

ANSWER.—The salutary effect of acute febrile disease on allergic manifestations has been known for centuries. Chronic and intractable asthma frequently becomes more completely relieved by intercurrent nonrespiratory infection than by almost any other means. It is not certain whether the elevated temperature or the conditions causing it (tissue destruction, bacterial substances, hormone production) are responsible for the benefit. Typhoid vaccine, injection of colloidal sulfur and malarial therapy have been used in the past. Fever produced by high frequency currents (diathermy) was used a number of years ago (Feinberg, S. M.; Osborne, S. L., and Steinberg, M. J.: Sustained Artificial Fever in the Treatment of Intractable Asthma, *J. A. M. A.* **99**:801 [Sept. 3] 1932). More recently a pure carbohydrate constituent obtained from certain bacteria and known as pyromen® has been used to produce fever. An intravenous injection of 1 to 50 gammas will produce fever and other symptoms. While any of the above methods may relieve asthma, most of them are not without danger. They must be used with great caution, and the results are apt to be temporary.

COMPENSATION IN PARTIAL LOSS OF VISION

To the Editor:—What modification of the standard percentage of visual efficiency or loss is made in the case of slight impairment affecting one eye when vision in the other eye has already been impaired from pre-existing and nonrelated disease? What modification is made depending on the visual level of the other previously impaired eye? The case in point is one in which the right eye carried a vision level of counting fingers owing to a previous disease. Years later retrobulbar neuritis developed involving the left eye, reducing vision to a 20/70 level after correction, with a permanent residual scotoma involving the central fixation area. This condition is compensable under the terms of the patient's private health and accident disability insurance. The percentage loss in visual efficiency according to the American Medical Association standards in this case would be about 33 to 35 per cent. But I wonder whether the percentage loss should not even be greater for a person whose vision in the other eye was practically serviceable previously. It seems to me that a 30 per cent loss in his only remaining eye is a far greater tragedy to him and actual disability than would be the case if the remaining eye had a normal level or a more moderate impairment. I think the standard percentage for visual loss in a case like this should therefore be modified, but I am not in possession of any tables showing what modification is reasonable. I would appreciate enlightenment on the subject.

H. Weldon Wilkinson, M.D., San Jose, Calif.

ANSWER.—Tables reducing disability to definite percentages are useful as a guide in some cases but inadequate in cases such as this. After the evidence is presented by the plaintiff and the defendant, the judge has to decide and usually allows much more than the percentages suggested by the Committee on Compensation of the American Medical Association. Different occupations require different degrees of visual acuity; what might be a serious loss to one would be only a moderate loss to another, although algebraically they might be equal.

PIGMENTATION FOLLOWING TREATMENT FOR ACNE

To the Editor:—A Negro woman who is being treated for acne of the face now has darker pigmentation of the treated areas. Is there any safe bleaching agent that may be used on the patient's face? The acne has improved.

M.D., Ohio.

ANSWER.—Melanosis following actinic ray application may occur in any racial group. Such occurrence has been observed frequently after one treatment, but it usually becomes pronounced after the third. The sulfur content of the skin and the use of sulfur or sulfur-like preparations either before or during therapy seem to be the chief contributing factors. One may prevent or alleviate the condition by (1) prohibiting or reducing the intake of sulfur-containing foods during the treatment period, (2) carefully and thoroughly cleansing the skin before treatment and (3) refraining from the use of sulfur-containing preparations for the duration of treatment. If left alone the melanosis will disappear in six to 12 weeks; mild skin peeling will hasten the process. An ointment of 2 per cent salicylic acid and 10 per cent ammoniated mercury in a greaseless ointment base is satisfactory. This application is to be made and removed immediately when tingling is noticed and then reapplied on the following day. Treatment should be repeated until desquamation occurs.

PRUNE JUICE AS A CATHARTIC

To the Editor:—I have a sample of prulose®, which apparently contains 2 grains (0.12 Gm.) of dehydrated prune concentrate, 6 grains (0.40 Gm.) of methylcellulose and 1/63 grain (1.03 mg.) of diacetyldioxyphenylisatin. It was stated that this last-named drug is the cathartic agent in prunes. I would appreciate knowing whether this drug is prepared synthetically or by the processing of prunes. If it is not the cathartic principle of prunes or prune juice, what might it be?

Walter A. Fansler, M.D., Minneapolis.

ANSWER.—According to Emerson (*Proc. Soc. Exper. Biol. & Med.* 31:278, 1934) water extracts of prunes possess certain chemical and physiological properties similar to dihydroxyphenylisatin. Emerson also found that, while diacetyldioxyphenylisatin (isacen) had effects similar to prune extracts on the isolated gut, the compound, unlike prune extracts and dihydroxyphenylisatin, did not give a positive reaction in the ferric chloride test for phenolic groups. Diacetyldioxyphenylisatin, a phenolphthalein derivative, was synthesized by Guggenheim in 1925 in a search for a more effective cathartic agent than phenolphthalein. He found it to be less irritating to the stomach than the parent nonacetylated compound. It was accepted by the Council of Pharmacy and Chemistry in 1926 but omitted in 1940 because of lack of clinical evidence that it possesses any demonstrated superiority over phenolphthalein and because it was more expensive than phenolphthalein.

IMMUNIZATIONS IN OLDER PERSONS

To the Editor:—Preparatory to traveling to South America, a man and his wife asked me about typhoid, paratyphoid and typhus vaccination. Are there any contraindications? The man is 60 years old, had typhoid when he was 12 and is a mild diabetic. He has arteriosclerosis, blood pressure of 160/95 and retinopathy which has been stable for several years. His wife, 65, had a mild cardiac attack several years ago, with residual low cardiac tonus.

M.D., New York

ANSWER.—It is unlikely that a 60 year old man who has had typhoid would experience another attack and he might have an unpleasant reaction if given typhoid vaccine. It seems reasonable that this man, in his present condition, not be subjected to any immunizing procedure which is not urgent. Although typhoid is not common at 60 to 65 years of age, it is advisable to afford the wife protection. If the intracutaneous method is used, the possibility of severe reactions is lessened. The couple should not be denied protection from typhus if they are going to a locality where typhus is either epidemic or endemic.

VITAMIN C AND CATARACTS

To the Editor:—Is there any scientific evidence to show that the continuous and prolonged oral use (more than one year in the case in question) of 300 mg. daily of ascorbic acid can produce opacities of the crystalline lens?

M.D., New Jersey.

ANSWER.—There is no clinical or experimental evidence that human beings experience any toxic effect from vitamin C given in the dosage mentioned. Vitamin C plays an important part in the nutrition of ocular tissues. The healthy lens is particularly rich in this vitamin, while totally cataractous lenses contain little or none. There is evidence that vitamin C has no direct bearing on the experimental production of cataract but no evidence that an excess of it contributes to the development of cataract.

VAGINAL PROLAPSE

To the Editor:—What is the incidence of vaginal prolapse following vaginal hysterectomy for uterine prolapse in general and particularly after Heaney's operation for prolapse? What are the best operative methods for vaginal prolapse following vaginal hysterectomy?

I. Andrussier, M.D., Philadelphia.

ANSWER.—Vaginal prolapse after vaginal hysterectomy is rare. Veenboer and Kooistra (*Am. J. Obst. & Gynec.* 53:936 [June] 1941) followed 104 cases of vaginal hysterectomy from 18 months to four years and found no cases of vaginal prolapse. However, Rhoads and Zeit (*Am. J. Obst. & Gynec.* 51:533 [April] 1946) followed 385 vaginal hysterectomies according to the technic of Weir and found four cases of prolapse of the vaginal vault (2.08 per cent). Some gynecologists have performed several hundred vaginal hysterectomies without the occurrence of prolapse of the vagina, and this is true of the Heaney technic; but prolapse of the vagina following vaginal hysterectomy is a definite possibility. Vaginal prolapse must be differentiated from enterocele.

There are two ways of attempting to cure prolapse of the vagina, one of which employs the abdominal route and the other the vaginal route. The abdominal operations of suspending the vagina to the abdominal wall are generally not satisfactory. Much better results are obtained by an extensive vaginal plastic operation including suture of the posterior vaginal fascial layers and the building up of a strong levator sling and perineal body. In very old women partial or complete colpocleisis may be done.

ARTHRITIC CHANGES OF OLD AGE

To the Editor:—Is the use of desoxycorticosterone acetate warranted in the treatment of the hypotrophic arthritic changes of old age in which the cause is obscure?

M.D., Mississippi.

ANSWER.—Rheumatologists are almost unanimous in their opinion that desoxycorticosterone acetate does not exert a beneficial action on any type of arthritic process. Furthermore, its potential hazards in hypertensive and cardiac patients, because of salt and water retention, must not be overlooked. Because of the many cardiovascular and renal changes in old age, desoxycorticosterone acetate must be used with caution when indicated.

POSTNASAL DRIP

To the Editor:—A patient with chronic sinusitis of many years' duration has nocturnal postnasal drip. He awakens from sleep to expectorate the material about twice nightly. Being awakened he voids. This nocturia was ascribed to prostatic hypertrophy. I considered the nocturia as pseudonocturia, since no prostatic enlargement was found. I prescribed 50 mg. of diphenhydramine hydrochloride before retiring, with splendid response. Occasionally, the patient forgets to take the drug and his sleep is again interrupted as aforementioned. The patient believes that he has become addicted to this drug. I reassured him that this drug, in the dosage given, is not habit forming and that it would not cause "liver damage."

M.D., New York.

ANSWER.—While diphenhydramine hydrochloride is the most sedative of the antihistaminic drugs, as yet there are no reports in the literature of addiction to the drug because of this effect. Long term use of any sedative may lead to dependence. Experimental evidence indicates that detoxification of diphenhydramine probably occurs in the liver, spleen and kidney, with the liver playing the primary role. Chronic toxicity studies have failed to disclose definite liver damage due to this drug, but effects on the hemopoietic system have been noted.

HAMSTERS FOR CULTURING TUBERCULOUS MATERIAL

To the Editor:—In *The Journal* of July 22, 1950 (page 1127) in response to a query as to the possibility of using hamsters instead of guinea pigs for inoculation of possible tuberculous material, it is stated, ". . . the culture is much cheaper and in a number of ways more efficient and direct." I feel that many of the men dealing with tuberculosis will not agree with that statement.

The culturing of sputum or gastric contents may be a bit cheaper than inoculating a guinea pig, but I believe it is far less reliable. Cultures are difficult to grow and must be interpreted by experienced laboratory personnel. I find that about 5 per cent of gastric lavages reported as being negative on culture are positive on guinea pig inoculation. This is especially true in cases in which there has been adequate collapse and chemotherapy. Of some dozen veterans recently discharged from a Veterans Administration hospital, all of whom have had literally dozens of negative gastric cultures, three have been found to have negative cultures, but guinea pig inoculation of the same specimen was positive. In a matter as vital as this, a small additional expense should not stand in the way of certainty of ruling in or out the presence of active tuberculosis or of giving the patient a false sense of security.

Elliot A. Rouff, M.D., Los Angeles.